69.3

REVIEW OF GOVERNMENT SUPPORTED RESEARCH ON AGING

VOLUME III

APPENDIX B - PART II

APPENDIX C

APPENDIX D

69.3

APPENDIX B - PART II

VETERANS ADMINISTRATION PROJECTS

A.F. Abt and S.L. von Schuching
Veterans Administration Hospital
Martinsburg, West Virginia
The Influence of Nutrition on
Bone Healing

Rene Albacete
Veterans Administration Hospital
Washington, District of Columbia
Aging Research

George Anday
Veterans Administration Center
Los Angeles, California
Chromosomes in Old Age

Max Apfeldorf
Veterans Administration Center
Martinsburg, West Virginia
Electroencephalographic (EEG)
Rhythm and Auditory Reaction
Time as Functions of Aging

Max Apfeldorf
Veterans Administration Center
Martinsburg, West Virginia
Minnesota Multi-Phasic Personality
Inventory Responses, Antisocial
Behavior in Aged Maladjusted
Subjects

Joseph Barboriak
Wood Veterans Administration Center
Wood, Wisconsin
Effect of Aging on Alcohol Tolerance

Benjamin Bell
Veterans Administration
Outpatient Clinic
Boston, Massachusetts
Normative Aging Study
(See Appendix C)

Rayman Bortner
Veterans Administration Center
Hampton, Virginia
Laboratory Risk-Taking Behavior

Rayman Bortner
Veterans Administration Center
Hampton, Virginia
Stages of Adult Development

F.L. Brochu
Veterans Administration Hospital
Dallas, Texas
Response of Extracellular Fluid and Red Cell Volumes to Surgery

D.L. Buchanan
Veterans Administration Hospital
West Haven, Connecticut
Metabolic Origin of Beta-Aspartyl Peptides

Robert Canestrari
Veterans Administration Center
Hampton, Virginia
Verbal Learning

Robert Canestrari
Veterans Administration Center
Hampton, Virginia
Cerebral Circulation and Behavioral Deficit

Thomas Capers
Veterans Administration Hospital
Dallas, Texas
Cooperative Studies in Pathology
Cooperative Study on Aging in Men: A Morphological Study
I Endocrinological Aspects

Arthur Cherkin
Veterans Administration Hospital
Sepulveda, California
Aging and Memory

Sidney Cleveland
Veterans Administration Hospital
Houston, Texas
Psychological Aspects of Aging

Sylvia Coleman
Veterans Administration Center
Bay Pines, Florida
(1) Changes in Aging Populations of Bacteria
(2) Possible Role of the Mycoplasma Group of Bacteria in Degenerative Diseases and Aging

(3) The Formation of L-Type Growth in Senescent Cultures as well as the Relation of L-Forms and Photoplasts of Bacteria to Chronic Disease

James Conner
Veterans Administration Center
Bay Pines, Florida
(1) Effect of Magnesium Pemoline on Cerebral Function and Physiological Responses in Human Subjects
(2) Effect of Autonomic Nervous System Blocking Agents on Adaptation in the Elderly

Neil Coppinger
Veterans Administration Center
Hampton, Virginia
A Collaborative Study of Automated Assessment of Psychological Deficits

Robert Davis
Veterans Administration Center
Bay Pines, Florida
(1) Effect of Maternal Dietary Deprivation on the Aging of Progeny
(2) Vitamin B_{12} Metabolism in Aging Populations
(3) Study of Effects of Nutrition and Aging on Bacterial Cell Surface Sites Reactive to Nucleic Acids, Vitamin B_{12} Antibiotics, and Other Compounds
(4) Serum Enzyme Studies of Different Aging Populations

James Dolson
Veterans Administration Center
Bay Pines, Florida
Gerontological Research in Social Work Service

Allen Edwards
Veterans Administration Center
Los Angeles, California
Prophylactic Psychopharmacology
and Age-correlated Intellectual Changes

Seymour Fisher
Veterans Administration Center
Los Angeles, California
Immunization to Influenza, Diphtheria and Tetanus, Duration and Intensity of Protection

Eugene Frenkel and Richard Sheehan
Veterans Administration
Aspects of the Radioisotope-Hematology Research Program as it Relates to Aging

J.L. Haining
Veterans Administration
Jackson, Mississippi
The Regulation of Intracellular Protein Metabolism During Development

Hans Hoch and Thomas McGavack
Veterans Administration Center
Martinsburg, West Virginia
Iodine in Serum
I. Qualitative and Quantitative Appraisal
II. Changes with Age and Thyroid Status

Walter Hogan
Wood Veterans Administration Center
Wood, Wisconsin
Gastric Secretory Capacity in the Normal Aging Population
Gastric Secretory Function in New Duodenal Ulcer Patients Over 50

Richard Huemer
Sepulveda Veterans Administration Hospital
Sepulveda, California
Developmental Biology of Aging

Leonard Jakubczak
Veterans Administration Hospital
Jefferson Barracks, Missouri
Gerontological Psychology Research

Harold Koenig
Veterans Administration
Chicago, Illinois
(1) Effect of Analog-Substituted RNA's on Protein Synthesis
(2) Studies of Neural Lysosomes

Raymond Lindsay
Veterans Administration Hospital
Birmingham, Alabama
Effects of Aging and Hormones on Pyrimidine Utilization for Nucleic Acid Synthesis

Robert Lindeman
Veterans Administration Hospital
Oklahoma City, Oklahoma
The Effect of Surgical Trauma on Renal Excretion of Calcium, Magnesium and Zinc

Margaret Linn
Veterans Administration Hospital
Miami, Florida
(1) Nursing Home Studies
(2) Aging and Socio-Environmental Stress
(3) Physical Resistance in the Aged

T.H. McGavack and E.C. Trout
Veterans Administration
Martinsburg, West Virginia
Effect of Thyroid Hormone on the Production and Peripheral Transformation of Steroids in the Aged Individual

T.H. McGavack and E.C. Trout, Jr.
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Formation of Ketosteroids by Adrenals of Young and Old Guinea Pigs

T.H. McGavack and K.Y.T. Kao
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Martinsburg, West Virginia
Aging in Connective Tissue II.
Ground Substances
a. Urinary Carbohydrate-Protein Complexes (CPC)

T.H. McGavack and K.Y.T. Kao
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Martinsburg, West Virginia
Aging in Connective Tissue II.
Ground Substance
b. Changes in the Composition of Ground Substance During Aging

George Magid, Robert Hansen and Harold Murdock
Veterans Administration Hospital
Livermore, California
Gastrointestinal Absorption of Calcium in the Male Using Calcium 47 and Calcium 45

M.P. Murray
Wood Veterans Administration Center
Wood, Wisconsin
Studies of Normal and Abnormal Motion

Hans Naumann
Veterans Administration Hospital
Memphis, Tennessee
Chemical Changes of Aging

Saul Needleman
Veterans Administration Research Hospital
Chicago, Illinois
Amino Acid Analogs and the Etiology of Collagen Disease

Edmond Phillips
Veterans Administration Hospital
Jefferson Barracks, Missouri
The Relation Between Social Behavior Pattern and the Functional Aging of Humans

Lajos Piko
Sepulveda Veterans Administration Hospital
Sepulveda, California
Properties and Function of Mitochondrial DNA in Relation to Development and Aging

Hubert Pipberger and Edward Freis
Veterans Administration, Washington, D.C
Demonstration of Aging Processes of the Cardiovascular System by Non-Traumatic Recording Methods

Vladimir Pishkin
Veterans Administration Hospital
Oklahoma City, Oklahoma
Auditory Concept Identification as a Function of Age and Sex

Clayton Rich
Veterans Administration Hospital
Seattle, Washington
Versine Infusion Test in Osteoporosis

Frank Schlenker, Julio Goldenberg and Michael Gompertz
Veterans Administration Hospital
Memphis, Tennessee
Biochemistry of Intestinal Tissue

Ernest Schwartz
Veterans Administration Hospital
Bronx, New York
Clinical Physiology of Bone: Effect of Hormones and Vitamin D

Sant Sekhon
Veterans Administration
Long Beach, California
The Process of Aging in the Central Nervous System of Mouse

Marott Sinex and Robert Herrmann
Veterans Administration Hospital
Bedford, Massachusetts
Age-Related Differences in DNA and Deoxyribonucleoprotein

Stanford Simon
Wood Veterans Administration Center
Wood, Wisconsin
Performance on a Motor Steadiness Battery as a Function of Chronological Age with Older Normal Domiciliary Members

Maurice Sklar
Wadsworth GM and S Hospital
Los Angeles, California
Psychoacoustic Parameters of Presbycusis

Raymond Smith
Veterans Administration Hospital
Seattle, Washington
The Effect of Varying Signal-to-Noise Ratios on Speech Discrimination Ability as a Function of Age

Harry Sobel
Veterans Administration Hospital
Sepulveda, California
Age-Associated Changes in the Skin and Their Systemic Metabolic Equivalents

Anthony Soldo
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Miami, Florida
Effect of Radiation on Aging, Protein and Nucleic Acid Synthesis

G.H. Stidworthy
Veterans Administration Hospital
Bedford, Massachusetts
Biosynthesis of Glycosaminoglycans and Aging in vitro and in vivo

Paul Thornton
Veterans Administration
Lexington, Kentucky
Bone Tissue Metabolism as Influenced by Aging Factors

David Tice
Veterans Administration Hospital
New York, New York
Follow-Up of Aged Patients who
Undergo Surgery

Harry Walter
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Long Beach, California
Differentiation of Young and Old
Protein Molecules and Separa-
ation of Cells and Particles by
Counter-Current Distribution

Kuang-Mei Wang
Veterans Administration Hospital
Buffalo, New York
Relation of Age to Protein Synthesis
and Enzymatic Activities

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Little Rock, Arkansas
Arylsufatase in Normal and
Diseased States
Cooperative Study - Morphological
Changes
I. Endocrine System

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The Influence of Nutrition on Bone Healing

This investigation was initiated as a project to study the influence of nutrition on bone healing. Since aging has such a retarding effect on bone union, a careful separation of the experimental animals, according to age level, is part of the protocol.

It is difficult to assess bone healing and the influence of various nutritional constituents following fracture in experimental animals. The methods previously employed in animal experimentation were tests devised to measure the mechanical breaking strength of the fractured bone. Bauer was the first to use radioactive calcium in a study of bone following fracture. It was, therefore, determined to use radioactive calcium as a measure of the progress of bone healing and fractures. An application to the healing of human fractures would be an early diagnosis and prognosis of nonunion. The occurrence of nonunion increases with age.

The development of the concept of bone remodeling has demonstrated that we are dealing with two related processes:

1) Synthesis and resorption of the organic matrix.
2) Synthesis and resorption of the mineral phase.

It is the balance between the rates of synthesis and resorption of matrix and bone which determines the remodeling of bone. These rates are in balance in normal adult bone although they differ not only from bone to bone in the same individual, but also in the various portions of a single bone.

Following fracture, profound changes in bone metabolism occur. New matrix forms the fracture callus and additional calcium is then deposited in the fracture callus. The fracture callus undergoes further transformation until it is absorbed and new bone fills the fracture gap. Studies with radioactive calcium have shown that in contrast to the increased mineral deposition in the region of the fracture callus, resorption of bone occurs at locations adjacent to the fracture as well as at other locations in the rest of the skeleton. Increased bone resorption is ascompanied by an increased bone synthesis.

In this study we are primarily concerned with the formation and turnover of the matrix in the fracture callus. We decided to use radioactive calcium as an indicator of the turnover of the fracture callus. Various time intervals from injection of the label to sacrifice were chosen. Guinea pigs were chosed as the experimental animsls since, analogous to the human, they are unable to synthesize

Vitamin C. The amount of collagen produced is influenced by the nutritional level of Vitamin C. The turnover of calcium which is interrelated with the turnover of the matrix is then altered.

The pattern of calcium turnover of guinea pigs of varying age levels and on varying dietary intakes of ascorbic acid before and following fractures should allow us to arrive at the optimum level of ascorbic acid intake for fracture healings.

Due to the complexity of calcium metabolism and the numerous variables which make the interpretation of findings difficult, several experimental approaches are used.

Autoradiographic studies have been performed on bones of guinea pigs, using radioactive ascorbic acid and calcium. The results demonstrate a very similar distribution of the labeled ascorbic acid and calcium.

Radiochemical determination of 45-calcium and 47-calcium in intact and fractured bone in guinea pigs on varying levels of dietary ascorbic acid intake are being performed. Samples for the determination of radioactivity are taken from blood, whole bone, and different fractions of the bone.

Radiochemical determinations of L-(1-^{14}C) ascorbic acid in intact and fractured bone have also been determined and will be compared with the calcium data.

Determination of whole body retention of 47-calcium in intact guinea pigs with experimental fractures is been conducted. Calculation of exchangeable calcium pool and accretion rate under the various experimental conditions as outlined is being carried out.

Rene Albacete
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Aging Research

A study of motility abnormalities of the esophagus is being performed in patients over 60 years of age without x-ray evidence of hiatal hernia. In these cases an acid infusion test of Bernstein, biopsy of the lower esophagus, with multipurpose Rubin tube, esophagoscopes and cinefluoroscopy. In those cases presenting marked motor abnormalities of the esophagus a clinical and x-ray study is made seeking for evidence of episodes of aspiration pneumonia.

The aim of this study is to investigate if the motility abnormalities of the esophagus frequent in the aging is related to peptic esophagitis. Also on the incidence of aspiration pneumonia.

George Anday
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Chromosomes in Old Age

In an effort to get a better understanding of aging chromosomes, a number of different studies were performed here and abroad during the past five years. It is entirely possible that the intricate mechanism of switching on and off genes plays a basic role in the aging process. It was deemed possible that such changes may become recognizable as numerical or structural changes of chromosomes. For the past eight years excellent chromosome techniques were developed including human lymphocyte cultures and such techniques opened up the field for this type of study.

As a first step, it appeared to be logical to examine randomly collected samples of different age groups of the population. It was hoped that if there are any characteristic changes of chromosomes in old age, they will appear at a certain age and will increase as age increases. Such cross-section studies are being conducted for the past 5 years by the Edinborough group in Scotland. Their results first indicated that with increasing age there was an increase in the proportion of aneuploid cells. The suspicion was expressed that in the aged, loss of a sex chromosome occurs. Such findings are intriguing since:

(1) it may indicate specific changes of aging,
(2) the chromosome-instability may explain the older age groups increased frequency of cancer,
(3) because the lymphocytes which were studied are of great immunological importance and could explain the increasing frequency of auto-immune diseases such as arthritis and decreased resistance toward infections.

However, the small number of such studies were already refuted by some investigators who found in a number of aged entirely normal chromosome complements. Court-Brown, who led the Edinborough group acknowledged (1967) that they have no sufficient material yet in such studies

Our own study started in 1964, before the Edinborough group's report was published. Our interest was aroused by two chance findings. In the one 90-year-old female the modal number of chromosomes was 45 and on closer analysis it was proven that the missing chromosome was a member of the C6-12-x group, probably one of the 2x chromosomes. The other observation was made on a 100-year-old male whose chromosome complements were normal; no abnormalities could be found in the number or the structure of the chromosomes and the aneuploidy was not greater than usual. This discrepancy was in our mind when

we read about the population study of the Edinborough group. We set out to do a similar morphological study but restricted to people over 80 years of age. Besides, we tabulated the chronic diseases of each individual, their blood groups and their electrophoretic patterns, since Waldenstrom claimed that aging is associated with immunoelectrophoretic changes. Since we do these latter tests routinely on our geriatric population, we could directly compare possible association of certain chronic diseases, electrophoretic patterns and blood groups with the chromosome studies. So far, we collected all these data on 71 patients ranging from 80 to 100 years of age, noting that some of these people were youthful and vigorous in spite of their age being over 90 whereas others were physically or mentally handicapped at the age of 80. With each of our chromosome cultures on the aged we included cultures of younger persons. This was not done to compare age differences; rather, to use them as controls for the technique and compare the aneuploidy which may be due to the technique. Our cultures were then harvested; slides were prepared and stained, covered with a cover glass. The photoing of karyograms and preparation of karyotypes proceeds at a slow rate since this requires a somewhat increased manpower. So far our results show that there is a great individual variation in the aged persons chromosome profiles. Structural changes were not significantly increased. Aneuploidy was highly over the usual 2-6% in some cases, whereas in others it showed low normal values. The most interesting finding was that in some individuals the main stemline was 45 with the consistent loss of a sex chromosome. In some others, so far studied, including a 100-year-old-male, only normal findings were present. In all these cases the patients were carefully checked for Barr-bodies to exclude hereditary sex chromosome abnormalities. In cases of positive finds we will now extend the study to skin cultures to see whether the abnormality involves cells other than the lymphocyte. We have not yet finished this study and no comparisons were made with the studied person's clinical findings and electrophoretic results. We think, whatever our final results are, it will greatly assist in creating a clear picture of how chromosomes appear in the aged. To this morphological study we plan to add a similar functional study on the mitogenic effect of the lymphocytes in old age. Bain et al showed in 1944 that lymphocytes of two different persons showed no mitotic activity without phytohemagglutinin (PHA); but, if the two cultures are mixed, the mitotic activity will be manifold, greater than if PHA would have been added to either of the cultures. Lowenstein et al reported that in such cultures the interaction of two different persons lymphocytes in the culture results in a substance which is transferred to the culture medium. We performed a few preliminary experiments with such mixed cultures. So far it appeared that two younger persons lymphocytes act as a forceful mitotic stimulant. We plan now to repeat such experiments in which an aged person's lymphocytes

will be also tested with each of the younger person's lymphocytes. Other ways to testing the reactivity and sensitivity of the aged person's lymphocytes are being planned.

Max Apfeldorf
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Martinsburg, West Virginia

Electroencephalographic (EEG) Rhythm and Auditory Reaction Time as Functions of Aging

Many investigators have reported that with the aging of the human organism there is a decline in intellectual functioning. The decline has been ascribed to decreased efficiency of the central nervous system and has been investigated in a variety of ways. The project, "EEG Rhythm and Auditory Reaction Time as Functions of Aging," has studied changes in the EEG alpha frequency, intelligence, and auditory reaction time in relation to some of the factors of aging and disease.

A progress report on the findings to date (Bauer, Apfeldorf, & Hoch, 1966) indicated that there was a decline in alpha frequency (a significant increase of brain wave period) with increasing age in 200 subjects with normal electroencephalograms. Patients aged 60 to 80 with a combination of heart and cerebral vascular degenerative disease differed significantly from other patient subgroups as to their rate of alpha frequency decline. Though there was a significant relationship between alpha frequency and intelligence in a group of 59 patients, this relationship appeared to be due mainly to the patients in the group who were diagnosed as having cerebral vascular degenerative disease, since excluding these patients from statistical analysis resulted in a disappearance of the significant relationship. A low but significant relationship between alpha frequency and intelligence was also found in subjects with heart disease and EKG findings.

The finding that the correlation between alpha frequency and intelligence in geriatric patients may differ in magnitude, depending on the disease of the geriatric patient, requires further study with larger and varied groups of patients. Therefore the study is continuing, despite the transfer of the Chief, Electroencephalography from the station. The focus of the investigation is no longer on reaction time, but on the relationship between EEG alpha frequency and intelligence.

As a first step, subjects are to be classified in terms of the arteriosclerotic dimension to determine to what extent the correlations

between EEG alpha frequency and intelligence are accounted for by arteriosclerotic factors. The subjects for the study will be classified by their physician on the basis of complete clinical examination as to the presence or absence of cerebral sclerosis and the presence or absence of peripheral arteriosclerosis. If cerebral sclerosis of clinical importance is present, it will be further divided into groups designated as: 1) acute, 2) subacute, and 3) chronic brain syndrome, and divided along another dimension in terms of the main artery affected: 1) carotid artery, 2) basilar artery, and 3) diffuse involvement. Patients with no evidence of cerebral or peripheral sclerosis will be divided into those having no other disease affecting CNS functioning and those having other diseases affecting CNS functioning. The classification system, as indicated below, yields 6 major groups and if further broken down by artery involvements 12 subgroups. The classification is backed up by relevant laboratory findings.

All subjects are to be referred for routine electroencephalograms administered with a 12 channel Medcraft machine. Alpha frequency is measured by taking 6 one-second samples from each of 5 runs of the electroencephalogram and averaging the 30 samples.

Intelligence will be measured by administration of the Wechsler Adult Intelligence Scale. In addition, memory functioning will be assessed by administration of the Memory for Designs Test and the Visual Retention Test, orientation by a specially devised questionnaire following the work of McAdam and Robinson, and some aspects of visual-motor functioning with the Bender-Gestalt and human figure drawing test.

An attempt will be made to match subjects in each of the classification groups in regard to age and education. The groups will then be compared with each other in regard to the EEG alpha frequency and the various intelligence test measures with the analysis of variance for matched groups or a similar non-parametric technique. If matching the subjects is not feasible, these control variables can be covaried in an analysis of covariance design.

To determine whether the alpha frequency and intelligence are related in any of the classification groups, product-moment correlation coefficients or similar non-parametric coefficients will be computed. Difference between correlation coefficients for the different groups can be computed through Student's t technique after applying Fisher's z' transformation to the correlation coefficients. Some technique for making multiple comparisons between coefficients, such as Tukey's, may be used.

Max Apfeldorf
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Martinsburg, West Virginia

Minnesota Multi-Phasic Personality Inventory Responses, Antisocial Behavior in Aged Maladjusted Subjects

This ongoing project is one of a series aimed at determining whether there are objective psychological characteristics that differentiate the elderly veteran with a record of disciplinary offenses from the veteran without such offenses. The purpose of the first project, "MMPI Responses of Domiciliary Members with Disciplinary Records" (Apfeldorf, Scheinker, & Whitman, 1966), was to determine whether a domiciliary group with a record of disciplinary offenses would be differentiated from a group without such offenses on the scales of the Minnesota Multiphasic Personality Inventory (MMPI), more specifically on the Psychopathic Deviate (Pd) Scale. However, the MMPI was also scored on all the other standard scales and three special scales, Adjustment to Prison (Ap), Ego Overcontrol (Eo), and Hostility Control (Hc), that had been found promising in other research on anti-social groups.

One of the interesting findings was that the offender and control groups were not differentiated on the basis of the Pd Scale. The lack of differentiation of the two groups on the Pd Scale raised the question whether the Pd Scale reflected anti-social activity in elderly, non-psychiatric subjects as well as it does in younger subjects. The Pd Scale was originally validated on psychiatric patients with diagnoses of psychopathic personality. Later it was found to identify subjects who had severe antisocial behavior that resulted in incarceration. It did not differentiate milder degrees of anti-social activity, as Remple found in his study of juvenile delinquents. It is quite possible that the Pd Scale, originally validated in a psychiatric population, is not an adequate differentiator for elderly subjects with milder degrees of anti-social behavior, consisting mainly of drinking behavior.

The offense group was differentiated from the non-offense group on the basis of three scales, the K suppressor, Lie, and Ego Overcontrol Scales, with the non-offense groups scoring higher on all scales. Two alternative interpretations were offered for the higher K scores of the non-offender group. On the one hand, following the usual psychiatrically oriented approach of the constructors of the MMPI, one could interpret the higher K scores of the non-offender group as reflecting their greater defensiveness. However, the screening procedure suggested that the group could not be considered akin to the usual psychiatric groups studied since they had reached old age without ever having received a psychiatric diagnosis. A number

of investigators working with nonpsychiatric subjects have claimed that K reflects, in these subjects, not defensiveness, but psychological health or self-acceptance. Further research using tests of self-acceptance and defensiveness, similar to those employed by Heilbrun and Smith, are necessary to determine definitively the interpretation of K in this sample.

In order to determine whether the scale differences between offender and non-offender groups are specific to subjects without psychiatric diagnoses, or conversely generalizable to those with psychiatric diagnoses, a repeat study is now being conducted in which both domiciliary members with and without psychiatric diagnoses are being tested. Two main groups of members with psychiatric diagnoses are being tested: a) neurosis, and b) alcoholism. The finding of scale differences specific to psychiatric groups would add support to the notion that different standards of interpretation are necessary within a heterogeneous domiciliary population.

All members in the domiciliary who have not been previously tested in the first project on disciplinary offenders have been considered subjects for the study. The Minnesota Multiphasic Personality Inventory is to be administered to the subjects in small groups. Prior to the MMPI administration, subjects are to be given the Vocabulary Section of the Shipley Institute of Living Scale to screen out those with a poor fund of vocabulary.

The primary statistical analyses will be similar to those conducted in the first project. Significance of difference between offender and non-offender groups will be determined by Student's *t* test. Separate *t*'s will be computed to determine differences between offenders and non-offenders within the following groups: a) neurotic reactions, b) alcoholism, and c) no psychiatric diagnosis.

If the offender and non-offender groups do differ significantly from each other on some relevant intellectual or demographic characteristic such as fund of vocabulary, education, age, occupational level, the significance of difference of MMPI scale scores can be determined by analysis of covariance techniques.

Joseph Barboriak
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Wood, Wisconsin

Effect of Aging on Alcohol Tolerance

A number of reports indicate that pharmacologic activity of various drugs is affected by the age of the recipient. Only a few data are available, however, which relate directly to the effect

of age on physiological responses to alcohol. In view of the increasing proportion of individuals entering the "retirement" category of our population, the knowledge about the possible age-induced impairment of alcohol tolerance would be of considerable practical importance. Our investigations concern two areas of possible age-alcohol interactions:

1. The effect of age on the alcohol-induced rise in blood lipids. This area was selected because of the reported association between high blood lipid levels and heart disease.
2. Modification of psychomotor reactions such as reaction time or postural stability by age and alcohol.

1. The Effect of Age on the Alcohol-Induced Rise in Blood Lipids

It has been known for a long time that some patients with chronic alcoholism develop high levels of blood lipids. More recent data indicate that alcohol, especially if taken before a meal, can increase blood lipid levels even in normal subjects. Our own data, obtained in preliminary studies, indicate that ingestion of two to four ounces of whiskey before a meal invariably increased plasma triglycerides over the levels seen after ingestion of the meal alone. In the present study we plan to investigate whether the lipemic response to premeal alcohol is more pronounced in persons over 60 years of age than in the individuals in the 20 to 35 year old bracket.

The subjects for the younger group will be recruited from among the medical and graduate students of the Marquette Medical School; the volunteers for the older group will be selected from the members of the Domiciliary Unit, Wood Veterans Administration Center, Milwaukee, Wisconsin. All participants will be interviewed regarding their general health and past drinking history. Subjects with abnormal liver functions, derangements of fat metabolism, poorly controlled diabetes, and persons showing dependence on alcohol will be excluded from the study.

In the experiment proper, the subjects will fast overnight and then receive 1.5 ml whiskey per kilogram body weight. The drink will be consumed within a 15-minute period. The subjects will then receive a nutritionally balanced meal containing about 60 gm fat. Blood samples will be collected immediately before the drink and one, three, six, and 24 hours after the meal. After a period of at least two days, the test will be repeated, but water will be given before the meal instead of alcohol. Blood alcohol levels and plasma cholesterol and triglyceride concentrations will be measured.

After obtaining the basic initial data, we plan to repeat the test with the same individuals for several years in order to find out whether the reactions to alcohol change with the progressing age of the subjects.

2. Modification of Psychomotor Reactions to Alcohol by Age

Little objective information is available about changes in alcohol tolerance with progressing age. In animal experiments, the lethal dose of alcohol was found to be lower for older groups than for the younger groups. A preliminary inquiry of number of older subjects concerning their alcohol tolerance showed the impression that they could "take their drinks better" when they were younger. We hope that the proposed study will provide more factual information about the effect of age on the responses to alcohol.

As in the previous study, subjects between 20 and 35 years of age will be compared with those over 60 years of age. After a light breakfast they will be tested for:

a. Body steadiness: The subjects will stand on a spring-supported platform. The swaying movements will be recorded.

b. Hand steadiness: The subjects will place a metal stylus in the center of progressively smaller openings and hold it there for 15 seconds. A contact of the stylus with the rim of the opening will be electrically recorded. Both number of contacts and time per contact will be considered.

c. Digit symbol substitution: This is a subtest of the Wechsler Adult Intelligence Scale and consists of substitution of symbols for numbers. The number of and correctness of symbol substitutions during a 90-second period will be considered.

After obtaining the initial information on the performance in the tests, the subjects will be given 1.5 ml whiskey per kg body weight and will be retested 30 minutes later. The alcohol-induced changes in test results will be evaluated.

We hope that results of the proposed study will contribute to our understanding of some of the problems relating to the physiologic and psychologic actions of alcohol in the aged.

Rayman Bortner
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Laboratory Risk-taking Behavior

An article recently submitted for publication by Dr. Bortner confirmed Brim, Glass, Lavin and Goodman's finding that belief systems are more significant for decision making than are general personality traits. Further, the study suggested that the relationship between value systems and decision making is different for verbal measures of risk taking and for measures which record actual choices in a laboratory. It is the latter, incidentally, which prove to be more related to actual behaviors in terms of decisions to enter or to leave a care-giving institution. It would appear that attitudes associated with internal locus of control would also be related to risk taking behaviors. That is the sense that one is captain of one's fate should be related to a realistic assessment of one's ability and of the situation. An internal locus of evaluation (feeling the best judge of the adequacy of one's performance rather than other people) may be of less significance. Finally, while such attitudes are undoubtedly influenced by early life experiences, they should also be age related. One of the controversies centering around disengagement theory is concerned with the degree to which disengagement is a reactive process, a giving up of ties and involvements because one feels that it is no longer possible to be captain of one's fate.

Data for this study were gathered as part of the recent data gathering in San Francisco. All of the sons had laboratory and verbal risk measures and loci of evaluation and control measures. In addition, some measures of value structure (the Arrow Dot subtest of the IES) were part of the Pattern A performance battery. Inter-correlations and another factor analysis should shed light on the relative role played by loci of evaluation and control in laboratory risk taking behavior.

The parents of the sons in this study responded to the Loci of Evaluation and Control Scale. Their scores will be correlated with age and with their responses to the life experience inventory. The partial correlation between age and loci of control with earlier risk taking behaviors held constant should tell us to what degree locus of control becomes more externalized with age.

We already know that choice behavior changes significantly with age. These studies will help us to add new dimensions to our understanding of these changes and, at the same time, give us a better understanding of the inter-relationships between attitudes, laboratory choice behavior and age.

Rayman Bortner
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Stages of Adult Development

Dr. Bortner recently published two papers which were theoretical rather than empirical in content. In one of these papers he examined the reasons for looking at adult personality change in developmental terms rather than as a purely idiosyncratic process. This point of view seems to offer a number of clinical and educational advantages and provides a theoretical context in which disengagement theory can be better understood.

In the other paper, he fitted this developmental conception into the context of social psychology and problems of environmental analysis in order to explore some research approaches to aging in the coming years.

In these papers he took the position that the importance of childhood experience was well established but it was not a sufficient basis for what happens in old age. A great deal of work has been devoted to noting which facets of personality are persistent and which are more subject to change. A reasonable conclusion seems to be that what is called character structure is fairly abiding save in the most profound disruptions of the balance among self perceptions, behavior and the behavior of others. The fact is that character structure sets up bounds beyond which "we cannot think, or imagine, or even dream" but most of our living is done at a more "superficial" level among the alternatives we <u>can</u> see, the memories we do have immediately accessible to recall, the dreams we <u>do</u> dream. These are most likely to influence our responses to the common transition points in life. For example, the Lt. Col. passed over for promotion and therefore facing either a long plateau or an early retirement, or the young parent facing whole new sets of responsibilities and behavioral expectations, have to respond by altering important segments of their behavior. Others treat them differently; the self concept must perforce be altered to some degree. We do not know the degree to which these kinds of transitions produce personality change; we do not know how common they are or how much disturbance in these habitual balances is helpful. We badly need empirical data.

There are a number of studies in the literature; still others are in the last pre-publication stages. Most of this work has been done and is being done at the University of Chicago. In order to familiarize himself and to gain access to appropriate samples for his own planned studies, Dr. Bortner has been offered and accepted a US Public Health Special Fellowship with the Committee on Human Development at that institution for a period of one year beginning in Sept. 1967.

The studies that he contempletes doing there will initially be exploratory in nature, dealing, for example, with pre and post event shifts in self perception among college students who are getting married or expecting their first child. These kinds of studies should lead to the selection of appropriate instruments for the examination of the psychological impacts of other events.

These studies are in the planning stage. Specification of methodology has to wait the choice or development of appropriate instruments. In general, the areas most likely to yield significant results are those of evaluation of self and others and of the future.

What happens psychologically from 20-60 years of age has become of increasing professional and popular interest. Unfortunately, there is too little empirical evidence to channel this interest into constructive educational and therapeutic programs.

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Response of Extracellular Fluid and Red Cell Volumes to Surgery

The measurement of red cell mass using dilution of administered radioactive chromium-tagged red cells, has become an accepted and useful clinical method in the practice of surgery. This is not the case with the measurement of extracellular fluid (ECF) volume, using the dilution of administered radioactive sodium sulfate as the parameter of volume. The initial aim of this project was to evaluate this latter method, using a technique originated in the Radioisotope Department of this institution. This involves a use of scintillation counting instead of the dry planchette method, and allows reporting of volume within hours instead of days. It was part of our aim to use patients, rather than "normal subjects," in this evaluation, to determine whether abnormalities of fluid balance would interfere with the measurement.

During FY 1966 and 1967 repeated studies were made on several patients in the preoperative period. The results were found to be reproducible and abnormalities of volume measurement were those to be expected in the clinical situation. The method has since been adopted at other institutions. Its use in healthy subjects, in a study for NASA, also demonstrated its technical reliability. Changes in extracellular fluid volume and of red cell mass have been reported coincident with major surgery or trauma. It appeared that the reported development of a "slowly circulating" red cell mass "compartment" might be related to the loss of extracellular fluid not accounted for at the site of injury. Pre and postoperative measurements of the two kinds of volume were made simultaneously in patients and in

animals. The qualitative changes in red cell mass could not be demonstrated.

Before reporting apparent changes in extracellular fluid volume coincident to major surgery, the derivation of volume, from the changes in plasma radioactively measured, was studied in detail, according to the method of Ryan. It became apparent that in the most unstable patients having clinical evidence of marked volume change, the method could not yield interpretable results in many instances. Use of a short cut method validated in normal subjects was shown to be very unreliable in sick individuals. The detailed calculations required for validation of method in each case, and a minimum yield of useful results, precludes the use of the radioisotope dilution method of extracellular fluid volume measurement in the average clinical situation. Objections to the method are qualitative, and inherent in the use of any radioisotope, since two basic assumptions are not possible in all cases, namely, constancy of volume, and reliability of plasma isotope concentration as an index of extracellular fluid isotope concentration, during the period of observation.

The study is continuing in two directions. The method is being used, subject to rigorous evaluation of each measurement, to study extracellular fluid volume loss in strangulating bowel obstruction in dogs. Here fluid loss into and around the strangulated loop is measurable; this loss is compared with total loss, in an attempt to determine whether a systemic shift of ECF is occurring.

The second avenue being explored, in surgical patients, is the ECF changes in geriatric patients as compared to that of younger individuals. ECF loss is being measured by clinical fluid balance, coincident with weighings of the patient, and also by the radiosulfate dilution method. To date there appears to be no difference in the response of the aged as compared to younger individuals.

The direction of change in either age group may not be that of net loss, and this is an important finding. While the aged patient is not different in his response, he is intolerant to error in therapy. A careful and accurate estimate of the amount and direction of change is essential in therapy of the aged, by whatever method is useful. In selected geriatric patients, the radiosulfate method may prove valuable, despite the very careful evaluation necessary each time it is used.

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Metabolic Origin of Beta-Aspartyl Peptides

After the discovery in this laboratory several years ago of a number of B-aspartyl di- and tripeptides other workers reported these compounds to be especially abundant in gelatine. They postulated that the B-aspartyl bond might be involved in the cross-linking of collagen chains known to occur in aging. Because of this and other suggestions that B-aspartyl bond formation could be a manifestation of protein molecular aging a study was undertaken to test the hypothesis. The B-aspartylglycine content of tendon collagen was studied in the human and in cattle but no difference was found between the young and old. There was also no increase with aging in solution of the B-aspartylglycine content of purified lysozyme.

Subsequent studies have greatly clarified the metabolic mechanism of B-aspartyl bond formation and there is at present no evidence that these chemical linkages are related to the aging process.

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Verbal Learning

Dr. Canestrari's interest in linguistic processes and the substantial deficit exhibited by aged persons in verbal learning situations even under self-paced conditions has led to an interest in the role of mediation in verbal learning. Riegel (1965) in his studies on speed of verbal performance demonstrated that association time is greater for the elderly as compared with young adults. Further, his data indicate that older subjects are more handicapped when they have to make associations when redundancy between test and response words are small. This is exactly the situation which obtains in paired-associate learning when the linkage between stimulus and response words is made deliberately obscure. For this reason an investigation of the use of mnemonic devices by young and elderly adults in paired associate learning was undertaken.

These devices appear to be employed extensively in this type of learning. Woodworth and Schlosberg (1954) refer to this tactic, but treat it as a contaminating variable. However, Miller, Galanter, and Pribram (1960) view the process as important in its own right. Underwood and Schultz (1960) also discuss this strategy and report a study with young adults that attests to its pervasiveness in a paired

associate task. Dr. Canestrari's own experience with elderly subjects was certainly not in keeping with this observation and a subsequent study in word association with young and elderly subjects from low socioeconomic and educational backgrounds indicated that when linkages were obscure the aged subjects gave significantly more multiple word and uninterpretable responses or omitted a response. In the previously mentioned study by Underwood and Shultz there were 280 pairs of words, and subjects reported they utilized no association in only 27% of the pairs.

There are several studies with young subjects which demonstrate the effectiveness of the use of such tactics in a paired associate task. Wallace and his colleagues (1957) instructed subjects to form a mental picture connecting each pair of words to be learned. They found that subjects were able to remember 99% of the word pairs presented with lists containing up to 500 items although the pairs were presented only once. Other studies (Gruber, Kulkin, and Schwartz, 1965; Paivio, 1965; Runquist and Farley, 1965) have also demonstrated that mnemonic devices have a facilitating effect in paired associate learning tasks.

However, the use of mnemonic devices by aged subjects has not received a great deal of attention until recently. There is some indirect evidence that older persons might encounter some difficulty in forming mental pictures or connections. This evidence comes primarily from studies in memory and creativity in aging. Jones (1959) comments that there is a reduction in the ability of older persons to form and integrate new connections. Several studies using a variety of approaches (Bromley, 1956; Prados and Fried, 1947) report an associative impoverishment among older persons.

In a more direct investigation, Hulicka (1965) found that elderly subjects reported using mediators less often than young subjects in a paired-associate task. In a subsequent study (1966) she found that older subjects reported 20% of the pairs were too odd to form a connection whereas the young subjects rarely complained of this difficulty.

Although older subjects have difficulty in developing mediators, Hulicka (1965) found that instructing them to do so resulted in improved performance. A pilot study in the laboratory also indicated that aged subjects could develop connections to some degree when instructed and that this ability was positively related to paired-associate performance.

Before going further it is necessary to point out that some studies make a distinction between verbal mediators and visual mediators. Dr. Canestrari and Franklin Knill set up a study to investigate the effects on performance of these two types of mediators in young and elderly persons. There was some evidence to suggest that

visual mediators might be more effective than verbal ones and that older subjects tended to rely on verbal mediators to a greater extent than young subjects. Further, Hulicka's work indicated that older subjects were less able to develop mediators than younger persons. For this reason a study was designed in which verbal or visual mediators were provided for each pair in the task. The goals were to see if performance could be enhanced by providing mediators and to see if the visual mediators were indeed more effective than the verbal mediators in elderly subjects.

Methods of procedure. Thirty elderly and 30 young adults were used in the first study. They were of comparable socio-economic backgrounds and educational level. A WAIS vocabulary subtest was administered to provide information as to intellectual status.

Following Canestrari's (1963) procedure, 30 one-syllable stimulus words were chosen from the Russell & Jenkins (1954) norms and paired with a response word that occurs only once in one thousand presentations of the stimulus word. These 30 pairs were randomly divided into three lists.

Simple sketches were made that contained both words of the pair. All, except two, were black and white with the exceptions being those accompanying the pairs "loud-tie" and "red-heart". The sketch for the former was done in color to depict a loud tie and the one for the latter was also done in color to depict a red heart.

A phrase was made up that contained both of the words. These phrases were very short, sometimes resulting from merely adding the indefinite article "a" to a pair - i.e., "a short box." Some phrases were in the form of equations: "Needle + nurse = hypo." In all cases except one the words were kept in the same stimulus-response order. The exception was with the pair "bed-twin" which was reversed to read "twin-bed".

Procedure - Condition I. Each subject was instructed that he would be shown a pair of words and that on subsequent trials he would be shown only the first word of the pair and asked to provide the second. He was also informed that previous studies had indicated that if a person sees a picture that contains the words it makes remembering easier. He was then instructed that such a sketch would accompany each pair and that he was to look at the pair and the picture.

Condition II. The subject was instructed concerning the presentation of pairs of words and was given instructions similar to those in Condition I with the word "phrase" being substituted for "picture".

Condition III. The subject was instructed only as to the procedure of presentation of the pairs and to the recalling of the response words. No instructions were given to induce any kind of strategy.

Throughout all the conditions on each trial subsequent to the first presentation each response word was shown again with the stimulus word regardless of the appropriateness of the subject's response. In Condition I and II the mediator was also shown each time with the stimulus and response words.

Trials for all subjects were presented under self-paced conditions. Subjects were instructed that they could take as much time as they liked to look at the pairs and to respond to the stimulus word. The time between the withdrawal of a pair together and the presentation of the next stimulus word was approximately five to ten seconds.

The dependent measure was the number of errors committed in reaching a criterion of one perfect recitation of a list. These errors were further broken down into errors of omission (no response) and commission (overt incorrect response).

Design. A Latin square design was used, whereby each of the two main groups were subdivided into three groups. Each of these sub-groups was exposed to each of the three lists and each of the three conditions. The order of presentation of the conditions was counterbalanced with the order of lists being disregarded.

Results. In general the study indicated that the providing of mediators significantly enhances performance. However, neither class of mediator was significantly different from the other.

This study led to a study on the effects of verbal and visual instructions to mediate, and standard instructions on the retention of paired associate lists.

Design. Essentially this design involves the comparison of the effects of four different treatments on retention after a 48 hour period of time. Eighty subjects were randomly assigned to each of the four experimental groups. During the course of learning a pair which was correctly responded to was immediately dropped from the list in order to more adequately test for retention. The dependent measure was the number of correct responses after a 48 hour interval. This study has just been completed and data analysis is underway.

A third study which has evolved from this general area involves the investigation of sustained instruction on the use of mediators in elderly subjects as compared with conditions in which the subject is simply told to mediate or is given no special instructions. Dr. Canestrari was particularly interested in the effects of sustained practice and instruction on the learning ability of older people. Further, the experiment was designed in the hope that it would reveal if the effect of instruction on the use of mediators

would generalize. That is, would the gains obtained under sustained instruction carry over to paired associate tasks run under the standard condition.

Design. Essentially the experiment has been designed to test the effects of the four previously mentioned treatments. The experiment consists of three stages: (1) all subjects will be given a paired associate task without instructions to mediate. This will serve as a baseline measure. Subjects in the first two groups will then be given specific training in the formation of verbal or visual mediators. Group 3 will be given instructions to mediate with an illustrated example and Group 4 will learn this list under standard conditions. (2) Groups 1 and 2 will then learn another list verbalizing the mediators they select for each of the pairs. Group 3 will learn this list with instructions to mediate and Group 4 will learn under standard instructions. (3) All groups will then learn a final list without any instructions. In this way we hope to see what effect specific and intensive training in the formation of mediators has as compared to instructions to mediate. Group 4 serves as a control group in order to obtain estimates of practice effects. The lists have been partially counterbalanced in order to take care of differences in list difficulty.

Dependent measures will involve error scores on first trial and to one correct recitation of a list. The first analysis will be a comparison of performance on the first list with performance on the second list across treatments. Analysis of covariance will be utilized if there are significant differences in groups on initial learning. The second analysis will be a comparison of performance on the second and third lists to see if the intensive training in the formation of mediators will be utilized and enhance performance in a situation where subjects are not forced to develop mediators.

At present this study is partially completed and several more weeks of running time will elapse before data analysis can begin.

Another study in the general area of verbal learning is being considered. The first study involves an investigation of an aspect of paced and self-paced schedules which has been neglected until the recent work of Troyer, Eisdorfer, Bogdonoff and Wilkie (1967). Their recent work suggests that a component of the paced schedule which may be related to performance deficit is the stress induced by rapidly paced schedules. The rapidly paced schedule could cause a deterioration because of an erasure phenomenon and because the older subject needs greater response time. However, performance could also deteriorate because the rapidly paced schedule is stressful enough to cause competing responses. A design is being considered which involves the utilization of a serial learning task with interstimulus intervals which vary in time duration. The reasoning is as

follows: If short intervals cause deficit behavior because of an erasure phenomenon or because of slowing in response speed, error scores ought to be confined to those elements of the list which have short inter-item intervals. However, if the deficit is in large measure due to a competing response based on anxiety or stress, the deficit behavior should extend to list members which directly follow items with short intervals even though the inter-item interval is one of increased duration. At present work is confined to selecting and placing intervals which would make an analysis of this sort feasible.

Significance. It is felt that the approach to learning deficits developed in this report represents a fruitful approach. In the past much of the research on aging has been of the type which catalogued the existence of a deficit. While it is essential to know where age differences exist, it is also important to attempt to understand the nature of the differences. Attempts which are geared to the manipulation of variables to reduce the amount of deficit ordinarily seen are of pragmatic as well as scientific value.

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Cerebral Circulation and Behavioral Deficit

The second major area of work currently in progress by Dr. Canestrari involves an attempt to obtain an index of cerebral blood flow and relate this index to current behavioral functioning. In recent years considerable attention has been devoted to the measurement of cerebral blood flow and cerebral metabolism as it changed with advancing age. A high degree of sophistication in procedure has resulted and it is now possible to obtain indices of cerebral vascular functioning. Because of the sensitivity of cerebral functioning to disturbances in blood supply, it has long been assumed that some of the behavioral changes exhibited with advancing age may be related to prolonged mild or moderate impairment in cerebral blood flow (McFarland, 1963; Lassen, Munck, and Tottey, 1957). Kety and Schmidt (1948) pioneered a technique which allowed the quantitative determination of cerebral blood flow. Unfortunately this technique involves procedures which are uncomfortable and somewhat hazardous for the elderly subject so that its usefulness is limited. In recent years several different techniques have been developed which can provide an indirect measure of relative changes in cerebral blood volume (Oldendorf, 1962; Jenker, 1962). Coupled with this advance in technique is some evidence which provides support for the hypothesis that cerebral blood flow may be linked to some of the behavioral deficit seen in older persons.

This interest in deficit behavior has led to an attempt to investigate the relationship between indices of cerebral blood flow and behavioral variables. Dr. Canestrari has utilized impedance plethysmography as an index of cerebral blood flow. The choice was dictated in part by relative ease of obtaining measures, the skills of the individual investigator, and safety of the procedures. Essentially the procedure is based on the assumption that changes in cerebral circulation can be related to changes in electric impedance of cranial tissue to high frequency (30,000 cycles per second), alternating current applied via electrodes placed on the scalp. The varying impedance due to pulsatile flow of blood is recorded by means of a polygraph, and measurements of various types can be obtained from the obtained wave forms.

Despite the large number of studies published utilizing impedance phethysmography (rheoencephalogram, hereafter identified as REG), the method is not without drawbacks. There is still little understanding of the causes and significance of the wave forms which are recorded. There is some question about the extent to which the measure is contaminated by flow through the external carotids. (McHenry, 1965; Lifshitz, 1963). However, recent work by several investigators (Seipel, Zemnowicz and O'Doherty, 1964; Namon, Gollan, Shimojiyu, Sano, Markovich and Scheinberg, 1967) provide strong support for the hypothesis that REG is not significantly influenced by extracranial circulation. For example, intravenous injection of nicotinic acid, which has relatively little effect on intracranial circulation but has a potent effect on extracranial circulation, had little effect on REG waves.

For some considerable period of time work on this project was hampered by the necessity of gaining recording skills and having to share equipment. With the purchase of our own polygraph and increased skill in recording techniques, work has progressed more smoothly. Because the technique has been utilized for clinical purposes in the past, Dr. Canestrari spent a considerable period of time trying to quantify the measures. At present he utilizes three measures obtained from the curve. Since there was relatively little information about reliability of the measures, he ran a group of subjects to obtain split-half reliability measures. These were quite high, ranging from .86 to .94. In addition, he ran a group (N=14) of newly admitted stroke patients in order to see if known changes in cerebral circulation were reflected by alterations in the wave form. There were definite wave form alterations on the side of the pathology.

He now is in the process of gathering REG data and behavioral data on a larger group of subjects. Essentially the design involves correlation of the various REG measures with the behavioral data. Behavioral measures have been selected on the basis of several criteria. In general, tasks have been selected which have been shown to be sensitive to CNS pathology and to age. Further, the

tasks will range from simple psycho-motor tasks to those involving complex cognitive functioning. The present set of tasks include psychomotor measures (RT tapping), learning tasks (paired-associate), perceptual-motor tasks (trails, digit symbol) vigilance or attentional indices (critical flicker fusion), complex cognitive tasks (Stroop). This battery is being utilized in the initial study, but is not considered complete, and may be modified in later studies as additional equipment and data becomes available.

Methods of procedure. The design as stated previously involves correlating the REG measures with the behavioral measures. At present he is running subjects ranging in age from the 40's to the 70's. In the present study he plans on collecting data on some 60 subjects. At present he has collected REG data on 40 odd subjects.

The REG procedures involve the use of a Parks impedance plethysmograph and a Grass Model 7 polygraph with EEG preamplifiers. A record is obtained from each hemisphere by placement of electrodes over the orbital ridge and on the mastoid process. Careful head measurement is necessary to obtain symmetrical placements. In addition, an ECG is obtained on each experimental subject. The technique involves the introduction of a 30,000 cycle AC current at 2 milliamps to each hemisphere. Recordings are obtained at three time constants and the measures are based on an averaging of ten wave forms. Actual running time is short (3 to 7 minutes), but preparation involves a 20-30 minute time period. Behavioral data is obtained after the physiological recording. The scoring of behavioral data does not constitute a problem as all tasks are standardized and scoring is relatively simple. Scoring of REG data is time-consuming as each of the curves has to be hand scored and averaged.

Significance. Dr. Canestrari recently completed a data analysis in which the REG measures of 43 subjects were correlated with the psychomotor tasks. In all, 24 correlations were computed and eight were found to be significant at the .01 level. He is quite optimistic that the technique will prove itself to be useful as an index of blood flow and will demonstrate relationships between cerebral blood flow and behavioral deficit.

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Cooperative Studies in Pathology
Cooperative Study on Aging in Men: A Morphological Study
I. Endocrinological Aspects

Morphologic studies on endocrine glands in relation to aging are meager. It is felt that the VA could provide many male autopsies at various ages in a large scale cooperative effort to fill this gap in medical knowledge. A preliminary planning meeting was held at AFIP in December 1962 between AFIP and VACO representatives. Nine participating VA hospitals submitted 168 autopsies at the end of 1963 for a preliminary pilot study. From this experience of the pilot study the current main study was planned.

Primary Purpose: To observe the morphologic characteristics, both gross and microscopic, of the endocrine glands and their target organs at various adult male ages, and within various disease categories; to evaluate and provide a description of the frequency of these characteristics in the various age groups and disease groups.

Secondary Purpose: To attempt to detect any trends or relationships in the morphologic data collected which might appear to reflect aging per se; trends which could be made the basis for future separate studies each designed to test some specific hypothesis.

Source of Cases: All autopsies of adult males which are performed under the immediate direction of or by participating pathologists in cooperating VA Hospitals, provided the examination is done within 24 hours of death if the body is not embalmed prior to the examination or the examination is done within 48 hours of death if the body is embalmed prior to the examination and the embalming is done within 12 hours of death. Of the above autopsies the following are included in the study.

a. All autopsies performed on persons less than 40 years of age at death whether the autopsy is complete or incomplete.

b. All complete autopsies on persons aged 40 through 49 at death.

c. Complete autopsies performed on persons aged 50 through 79 at death and with VA claim numbers ending in 1 or 5.

d. All complete autopsies on persons 80 years of age or older at death.

Procedures: Endocrine organs are trimmed, weighed and fixed. Microscopic slides are prepared on endocrine organs and anatomical alterations in these are entered on the protocol. These data are submitted to Central Office statisticians and are entered on IBM punch cards to be stored in computers from which statistics are then formulated and calculated and conclusions formed from the data.

Publication: Study is a cooperative VA effort and no results are to be published without full consent of participants. Overall results of study are not available at this station but will come from Central Office when study is completed.

From this Station

1966 - 39 cases
1967 - 46 cases
1968 - 1 month - 8 cases

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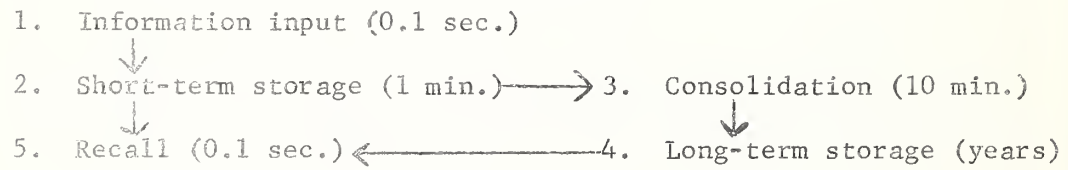
Aging and Memory

Aged brains do not remember well. They have special trouble in forming new memories; this creates costly problems for individuals and society. To add "life to our years, as well as years to our lives," we must learn how to preserve memory. Current efforts to improve declining memory are balked by our ignorance of normal memory; we do not have enough facts about memory processes to guide practical steps to preserve and improve them. We need new facts, to point the way to the nature of memory and to solutions of memory problems of the aged.

An old man remembers events of 60 years ago, but forgets where he left his keys 10 minutes ago. Such common observations, and many clinical and laboratory studies, suggest that the problem in the aged is not memory storage or recall, but the formation of new memories. By one theory, memory has five steps, with approximate time periods as follows:



Consolidation is the process most vulnerable to age. This new laboratory is interested to measure quantitatively its time-course and its temperature-dependence. Is consolidation a steady process? Does it start slowly, then accelerate? Or, does it start rapidly, then taper off (as most evidence indicates)? Does consolidation change with brain temperature in the same way as brain metabolism does, or differently? Once we learn quantitative answers to these questions, we can use them as yardsticks for present theories of memory, as clues to better theories, and as guides for electrophysiological and molecular studies.

Another inquiry is to study the exact effects of anesthestics upon memory. A partially anesthetized young brain behaves like an old brain: both can recall old memories, both can retain new memories for a few minutes, but both fail to make durable new memories. There is evidence that stimulant drugs can improve memory consolidation. The partially anesthetized animal is a promising laboratory model for quantitative studies of pharmacologic improvement of memory consolidation in the aged.

We have devised a quantitative "memory bioassay", utilizing the White Leghorn Cockerel, an agricultural waste-product that provides critical advantages over the laboratory rat or mouse. One thousand chicks cost less than 35 rats, permitting use of large numbers to increase reliability. Like man, the chick can learn quickly, its predominant sense is vision, and its active period is during the day. We have sources of highly inbred strains, to permit genetic studies. We can hatch chicks in the dark, to control precisely their total visual experience. We have shown that chicks resist, far better than rodents, the toxic effects of the treatments used to induce amnesia. Finally, the blood-brain barrier, that complicates drug studies in rodents, is absent in the chick. For these reasons, we consider the chick to be a highly advantageous subject for quantitative studies of memory consolidation.

Chicks peck at a small object spontaneously. If the object is coated with an aversive liquid, e.g., methyl anthranilate, a single peck is followed by avoidance behavior. We have quantitated this marked behavioral change and use it as a reproducible index of memory. At graded intervals after the first peck, we block consolidation of the memory by disrupting brain activity with a convulsant ether (flurothyl). The shorter the interval, the less the memory, when tested 24 hours later. We have determined a consolidation half-time of 14 minutes, that is, in 14 minutes after the learning trial, 50% of our chicks consolidate a memory trace, as indexed by our behavioral criterion (avoidance of pecking for 10 seconds). By varying the concentration of flurothyl vapor, we have confirmed the dose-dependence reported by others, using electroconvulsive shock, chemo-convulsants, and anesthetics. These findings have led us to announce a plausible interpretation of conflicting consolidation half-times. Our hypothesis is that short

half-times (less than 10 seconds) result from incomplete disruption treatments. If correct, it resolves a thorny controversy that confuses current memory research. It also points up the useful role of graded disruption in getting at the mechanism of consolidation.

We have completed our memory bioassay laboratory, with controlled environmental temperature, humidity, illumination and noise level, and have equipped our other laboratories. We have a well-trained staff, that tests 400 chicks per week, on a blind basis, with minimal supervision. Thus, we are in a strong position to define, under controlled conditions, the effects of variables such as strain, environmental conditions, learning strength, and disruption strength, and to generate the quantitative facts about memory that are our primary goal. With a tightly-controlled, well-studied experimental model in hand, we can proceed to study consolidation in partially anesthetized chicks, as a model of memory in the aged. After bringing our new laboratory to full staffing, we plan to examine the electrophysiological and biochemical correlates of our memory consolidation model. Hopefully, the facts developed in this multi-disciplinary, quantitative study of memory processes in a favorable animal will lead to insights useful in counteracting the decline of memory function in the aged.

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Psychological Aspects of Aging

As originally devised this study proposed to examine the subjective experience of aging, to describe the role of the self-concept in response to growing old and to trace the change in body image with advancing years. Interviews and psychological testing have been conducted with various groups ranging in chronological age from 47-72 years. To date a patient group comprising 45 members has been evaluated. This subject group consists of individuals hospitalized for a variety of medical reasons, all of which represent to some degree, difficulties in coping with problems of aging. A second subject group comprising 25 individuals experiencing no current difficulty in adjusting to their advancing years has similarly been studied.

Analysis of the interview data indicates that successful members of the aged group had by adulthood developed a feeling of completion and accomplishment in some area of life. Only those who had experienced a major failure in the area of behavior in which they had developed their feelings of competence spoke of feeling old. Others recognized their age but did not speak of being old.

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Changes in Aging Populations of Bacteria

Studies in aging have been approached by observing the characteristics of the aging process in populations of plants and animals, in organisms, in tissue cells, and in disease processes. From such studies many theories concerning the aging process have evolved, including theories of an accumulative aging factor, free radicals, stress, and others. The basic mechanism of aging must, however, begin at a cellular or molecular level. Of all cell populations, the simplest to cultivate and to quantitate are bacteria, and for this reason they have been used in many studies involved in growth and aging. One group of bacteria, the luminescent, has offered the opportunity to study easily the alterations in enzyme activity and cell function in selectively aged populations. In general, our research with bacteria has dealt with the quantitation of cell growth and function at the single cell level in aging. Some of the areas investigated are: (1) changes in aging populations of bacteria; (2) lytic properties of aging halophilic bacteria; (3) formation of L-type growth in senescent cultures; relation of L-forms and protoplasts of bacteria to chronic disease; (4) possible role of the mycoplasma group of bacteria in degenerative disease and aging. In the study concerned with the aging population of bacteria, the procedure followed was to inoculate cultures with identical numbers of cells from the same source and permit them to grow to three separate ages in the normal growth span of the population under the conditions chosen. These ages represented young, middle-aged, and senescent cells which are transferred consecutively to obtain populations which are never permitted to grow past a certain age. Thus, the young cells were never permitted to stop dividing, the stationary cells were taken several hours after active exponential growth had stopped and the senescent cells were taken after the population had begun to decrease due to the increased death rate. These microorganisms were also allowed to grow at three different temperatures, namely, 15^{o}, 25^{o}, and 30^{o} C, to compare the effects of temperature on the aging process. After every few transfers, several studies were made such as observation of morphological changes, measurement of endogenous respiration, and DNA/RNA content of cells and luminescent patterns. Cultures were allowed to grow to senescence over a period of several months. They were then transferred frequently to maintain logarithmic growth to determine whether the effects of senescence could be reversed by cell division. Our experiments have yielded results which demonstrate that the populations of young cells which were kept constantly dividing over long periods exhibit an increased cellular protein synthesis as reflected by the increased

luminescence. There were also physiological and morphological changes which were reflected by increased endogenous respiration, changes in cell size and RNA content. The longer the cell population was permitted to grow beyond the period of exponential growth, and the longer it was maintained at this growth phase, the greater was the loss of cellular enzyme activity. When the progeny of older populations were transferred to fresh media, they showed significant physiological deterioration which was not reversed after numerous transfers. Other areas of study would be the effects of radiation on these aging cell populations as well as the possible effects of free radicals on aging. These cultures could be permitted to age in the presence of easily reducible compounds.

Possible Role of the Mycoplasma Group of Bacteria in Degenerative Diseases and Aging

Another phase of research in microbiology concerns the possible role of the mycoplasma group of bacteria in degenerative diseases and aging. The mycoplasmas (PPLO) are being implicated in more and more disease processes. They are known to be the cause of primary atypical pneumonia, exudative pharyngitis, have been implicated in genito-urinary tract and joint disease and have been isolated from patients with rheumatoid arthritis and systemic lupus erythematosus. The first step of our studies of the possible role of mycoplasmas in degenerative diseases of aging has been to test the sera of some 200 patients of our Center, selected at random for the presence of significant antibody titers to three of the most common human species of mycoplasmas, namely, M. hominis, M. Pharynges, and M. pneumoniae. These microorganisms were cultured on the medium recommended by Chanock and co-workers and prepared as antigens for complement fixation and gel diffusion studies of patients' antibody titers and as vaccines for production of standard prepared antisera. The antigens were killed with formalin washed six times and suspended in saline standardized turbidmetrically and frozen and thawed ten times. The antisera were prepared by mixing a standard suspension of the organism, one to one with Freund's complete adjuvant and injecting rabbits alternately subcutaneously and intraperitoneally for ten injections. We have observed the presence of antibodies against these mycoplasmas in 10% of the 200 patients studied. These 10% have significant titers against the most common human species, M. hominis and only 1% - 2% against M. pneumoniae. The next phase of the study will be to attempt to correlate positive titers to specific groups of diseases. The virus-like intracellular growth of these bacteria presents an interesting host parasite relationship which could involve them in cellular changes in host organisms just as changes have been demonstrated in tissue cultures. With the capability of culturing these organisms now on artificial media, there is now opportunity

to study these unusual organisms in relation to the many disease processes for which no etiological agents have been observed.

The Formation of L-Type Growth in Senescent Cultures as well as the Relation of L-Forms and Protoplasts of Bacteria to Chronic Disease

The importance of the L-form bacteria is just being fully recognized. More and more these forms are being implicated in disease processes and latent infections. The L-forms of bacteria were first discovered and later defined by Klieneberger-Nobel. The importance of these forms in infection and other disease processes has been recognized.

L-type growth was selected from old cultures and also induced artificially by exposure to penicillin and bacitracin by cultivation on a sea water, horse serum medium containing elevated Mg^{++}. The growth forms were identified by their typical fried-egg type colonies and morphology and their growth in relation to Na^{+} and K^{+} concentration was studied quantitatively in relation to cell wall components remaining and to DNA/RNA ratios of the various forms. The hexose, hexosamine and diaminopimelic acid contents of the cell walls were determined as well as the DNA and RNA content.

In a separate study, the L-forms (protoplast forms) of pathogenic bacteria were looked at in relation to their role in chronic diseases common to the older veteran population. In particular, these forms were cultured from urine on special media to study their possible role in chronic urinary tract infections. The forms were correlated with the genera from which they were derived and with antibiotic therapy.

In studying the chemical changes in L-forms from halophilic bacteria, it was found that the DNA and RNA contents were not altered from normal cells, but the hexose diaminopimelic acid and in particular the hexosamine content were markedly lowered. The mechanism that triggers this alteration in growth form in senescent and other cells may be a key to the etiology of many latent disease conditions.

In our studies of L-forms into human chronic disease, it was found that special culture methods demonstrated the presence of protoplasts in the urines of 35% of the 120 patients tested who were diagnosed as having urinary tract disease. Over 20% of these were from the genera Pseudomonas and Proteus.

It is of interest to study the host-parasite relationship of these forms in a model system of pyelonephritis in the rat. The protoplast forms will be artificially produced and followed in the kidney over varying periods of infection.

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Effect of Magnesium Pemoline on Cerebral Function and Physiological Responses in Human Subjects

A psychopharmacological agent, Magnesium Pemoline (Cylert-Abbott) had been reported by Cameron and others to be effective in improving memory and cerebral function in animals and man. This study was designed to test the effect of the drug in human subjects having established clinical diagnosis of chronic brain syndrome and evident impairment of memory, judgment and other cognitive functions. The subjects were volunteer patients and members selected from the Domiciliary and Intermediate Service of the Center. After being properly informed of the purpose and other pertinent details, they were requested to sign a written consent form. A battery of psychological tests were administered as well as the Eisdorfer Serial Rote-Learning Test with monitoring on a multichannel polygraph before and after the treatment period. The supervisory nursing staff completed a Stockton Geriatric Rating Scale on each subject before beginning the treatment and weekly during treatment. The drug, Mg. Pemoline (Cylert-Abbott) was administered orally in 25 mgm. dosage once daily on a double-blind schedule with a corresponding placebo for a test period of 28 days. Appropriate laboratory tests were performed before, during and after the study to detect any evidence for toxicity or untoward reaction to the drug.

For this study, 29 patients with mild to moderate CNS dysfunction were subjects of a double blind paradigm. The 16 control (average age 76.5) and 13 experimental subjects (average age 71.3) were given 25 mgm. of the drug or inert placebo every morning for 28 days and examined for changes in learning, intelligence, memory, vigilance, physiological responsivity and ward behavior. For the Figure Embedment Test, the drug group improved significantly. On the nurses' rating (Stockton Geriatric Rating Scale) experimental subjects were shown to improve from week 1-5. For both variables, however, although the placebo groups's improvement was not significant, drug and placebo subjects did not differ on the final analysis. In all other respects, the drug group did not improve or tended to differ in an adverse direction. A paper is in the process of preparation for publication.

Effect of Autonomic Nervous System Blocking Agents on Adaptation in the Elderly

This project was carried out as a joint project in collaboration with Dr. Carl Eisdorfer and the Center for the Study of Aging at Duke University. The protocol was designed to test Dr. Eisdorfer's hypothesis that the anxiety generated in a laboratory learning test is exaggerated in the elderly subject, is accompanied by an excessive autonomic response, and the feedback of this response to the central nervous system has an inhibiting and disruption effect on the learning process.

A preliminary report of a partial analysis of the data submitted revealed the necessity to separate out the subjects into two groups -- a group that met all the rigid criteria and a group who failed in one or more of the criteria but were subjected to the study for the valuable information which it was felt could still be derived. The partial data analysis on ten subjects classified in the "good" group indicates that an adequate sympathetic autonomic blockade was achieved with both the beta and alpha adrenergic blocking agents as manifested by the physiological responses. This group was too small to offer statistical significance as regards the primary hypothesis; however, it does appear that the subjects that received the beta blocking agent did exhibit the higher degree of serial rote learning response accuracy. The physiological responses noted in the beta blocked group were characteristic of those which have been described in the literature, with the most striking responses being bradycardia, inhibiting of free fatty acid mobility under stress, and supression of the galvanic skin resistance. The subjects who received the alpha adrenergic blocking agent exhibited an exaggerated postural hypotensive response which was minimized by reduction in dosage and resorting to a semi-reclining position during the experiment.

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A Collaborative Study of Automated Assessment of Psychological Deficits

Four investigators have been enlisted in a program of collaborative studies of automated procedures for assessing age-related deficits in cognitive functioning. They are David Cohen, Ph.D. (Coatesville, Pa.), Max Apfeldorf, Ph.D. (Martinsburg, W.Va.), Eugene Chambers, Ph.D., (Dayton, Ohio), and N.W. Coppinger, Ph.D. (Hampton, Va.). These automated procedures (TAPAC - Totally Automated Psychological Assessment Console) were designed by Allan Edwards, Ph.D. (Los Angeles).

The interest in the automated assessment of age deficits in cognitive functioning should be viewed as an example of "research and development". It is atheoretical. While certainly expecting to have a rationale for their decisions which are based on educated guesses, past experience, and empirical data, they are not expecting to set up studies to test hypotheses growing out of either current theory or observation. This will come later after they first realize their immediate "R&D" aims. These aims may be broadly stated in the form of two questions.

(1) Is TAPAC a more effective system than those currently utilized for obtaining reliable and valid measures of the performance of older persons, either as patients to be assessed or subjects to be experimentally manipulated?

(2) Can a battery of measures be identified which can be automated and demonstrated to have maximum discrimination power in revealing age differences and changes in the several areas of cognitive functioning?

The extreme flexibility of the system permits stimulus complexity to range from visual and auditory sensory experience to self-reports of personality and social attributes. The response manipulandum is entirely motor but permits both simple and complex multiple choice decision making.

While agreement remains to be reached on the specific measures to be utilized, there is agreement on the concepts which must be included under the umbrella of cognitive functions. They will include both verbal and performance measures which are expected to remain relatively intact as one ages and those which one would expect to deteriorate with age. It would be highly desirable to select a battery of measures which are independent of each other or "factorially pure". Such, however, are not now known. The identification of such may be considered a primary aim of this undertaking. At this time the following measures are under consideration for investigation. They are - reading comprehension, vocabulary, information, short term memory, simple and disjunctive reaction time, intelligence, learning and concept formation. The "field test" of these measures will determine which should be retained, which should be discarded, and which additional ones should be examined.

Methods of Procedure. A description of the careful details usually expected for a methods section must be deferred until the physical meeting of the four collaborating investigators. This meeting is planned for the early Fall. At that time the specific questions to be explored will be operationalized and the *ad hoc* selection of measures completed. The initial phase of this project requires their developing and carrying out procedures which will provide answers for the following problem areas.

1. Edwards, as noted above, has determined the test-retest reliability of several of the proposed measures. Reliability must be ascertained for the additions. Some of the proposed measures are subject to practice effect. Therefore, alternate forms must be created and evaluated.

2. Performance based on recognition is usually superior to recall. TAPAC depends almost exclusively on recognition. How much, if any, discrimination power of a particular measure is lost as a consequence.

3. Some of the measures which have been proposed are automated versions of those commonly employed in either laboratory or clinical situations. The concurrent validity must be determined.

4. Previous work suggests that differences in the performance of groups differing with respect to age can be attributed to a host of

non-age variables. Examples would include differences in education, motivation, socio-economic status, speed, initial level of ability, physical health, etc. The contribution which each of these variables makes to the total variance will be examined both statistically and experimentally.

Significance. At the present time there is not available to the clinician or the researcher a set of reliable and valid tools for studying cognitive functioning in older persons. The present evaluation techniques being used by the practitioner are, at the best, inadequately standardized and at the worse, totally inappropriate to the problem confronting him. Much of the confusion and contradiction in the research literature can be attributed to inter-study differences in the experimental conditions. The availability of a system which permits precise control of the stimulus and response variables would do much for assuring the research investigator that his results reflect inter-subject differences rather than artifacts and contaminants in the experimental situation.

The particular significance and contribution which this project would make to the field of aging are several.

1. It would provide a battery of measures of cognitive functioning which have known reliability and validity.

2. Since the system is automated, the assessment setting is explicit and reproducible. Its system of control over stimulus and response variables will minimize inter-experiment and inter-epoch variability.

3. Deficits in cognitive functions are multidetermined. This project will provide baseline data on various criterion groups with age and age related deficits.

4. With the availability of this system the clinician will be in a better position to describe the assets and deficits of the older patient. The experimenter can proceed with greater confidence in his exploration and manipulation of the several sources of the differences and changes in older persons and in developing adequate theory for intergrating the results of his explorations.

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Effect of Maternal Dietary Deprivation on the Aging of Progeny

Restriction during gestation and lactation of the dietary intake of rats by as little as 25% of that consumed by an unrestricted group

results in growth stunting of the progeny, certain biochemical and metabolic derangements (Chow et al). This permanent growth stunting of progeny does not respond to an adequate diet fed on an unlimited basis after weaning. In collaboration with Dr. Chow, we are investigating in the rat and mouse the possible alterations in restricted progeny during the aging process. Such studies may throw some light on the ultimate aging patterns of children in underprivileged areas whose mothers ingest poor quality or inadequate quantity of protein during pregnancy and lactation.

Several of the objectives of this project include the studies of changes in body composition at different ages (1, 3, 6, 12 and 24 months); the immunological response to antigens during growth, maturation and senescence; metabolism and utilization of protein during aging and the isolation characterization of an abnormal polypeptide excreted by the deficient progeny.

In our studies of the effect of congenital malnourishment on the immunological response, our data strongly suggested that congenital malnutrition interferes with subsequent immune response. Sheep red blood cells were utilized in the first studies as antigen (in subsequent studies, crystalline egg albumin and other antigens will be used). The animals were immunized by the technique of Axelrod. We observed that maternal diet (protein) had some influence on the mode of agglutination titres. The animals (6) from Purina Chow fed mothers showed an average titre of 1:112; the progeny from wheat gluten (20%), 1:42; and finally, wheat gluten (80%) 1:28.

Mice will be studied at various intervals during their life span to determine the effect of age on the immunological response and in particular, the resistance to pneumococci Type 1 infection of mice with congenital malnourishment.

It is of interest to note that although the weight of the restricted progeny may be very similar to that of the controls, we observed that congenitally restricted mice when pair fed with controls lost significant amounts of weight. Such animals required significantly more food to maintain body weight.

Vitamin B_{12} Metabolism in Aging Populations

Earlier, we reported (Arch, Biochem & Biophys. 93:251, 1961) that vitamin B_{12} deprivation results in an elevated DPN/DPNH ratio and an accumulation of blood pyruvic and lactic acid in the rat. In view of the observed regression in serum vitamin B_{12} level with increasing age in humans as reported by a number of investigators including ourselves, we have investigated and are evaluating possible marginal vitamin deficiencies which may occur during the aging process, and as well, the possible effects of these marginal deficiencies on selected enzyme systems and metabolites. Several questions arise: are the lowered serum vitamin B_{12}

levels observed in a significant number of our aged domicile members (~50 mμg/ml) a physiological adaptation to decreased metabolic needs; what are some, if any, of the biochemical changes that may take place during aging when certain vitamins may be marginally deficient; and finally, are we physiologically correct in elevating any observed low levels of vitamins to the assumed higher levels of an earlier age. Fasting blood levels were obtained on large numbers of aged domicile members. In one study of 62 men, of average age 86 years, we observed significantly lower vitamin B_{12} levels than that of a younger group of domicile members. In fact approximately 15% of the aged group had serum vitamin B_{12} levels within the pernicious anemia range, possibly a reflection of a marginal vitamin B_{12} deficiency. Vitamin B_{12} serum levels of these subjects were measured on successive years with similar findings. In view of the apparent adequate nutritional intake of these aged subjects as verified by the clinical nutritionist, further studies were undertaken to determine whether this lower serum vitamin B_{12} level was due to poor absorption or some other mechanism and, if so, what biochemical systems were altered. Since several enzymes (lactic dehydrogenase and phosphohexoisomerase) were observed to be elevated in pernicious anemia, these determinations were performed as well as serum lactic acid. No significant changes were observed in these three determinations. In another experiment vitamin B_{12} absorption studies were performed on 60 subjects of average age 86 years who were administered vitamin B_{12} in various forms. Fasting blood samples were drawn under basal conditions, 6, and 12 weeks after vitamin administration and at later intervals. Our studies indicated no impairment of vitamin B_{12} absorption in this aged population. In view of the work of other investigators demonstrating that vitamin B_6 deficiency in the rat reduces the absorption of vitamin B_{12}, it well may be that this factor limits the absorption of vitamin B_{12}. We did observe the regressions of serum SGPT in both our Domicile and Intermediate Service subjects. Studies are in progress to determine whether the regressions observed are due to a deficiency of the coenzyme pyridoxal phosphate. Our studies indicate that although there is an agewise regression of vitamin B_{12} the subjects did not show any evidence of alterations in the serum enzyme or metabolite systems analyzed, nor were there any significant alterations in their hematologic profile. In fact the subjects with the very low serum vitamin B_{12} levels did not differ in their hematologic profile than the subjects with significantly higher levels of this vitamin. Our data indicate that the older person absorbs vitamin B_{12} and that the post administration increment is very similar to that of the younger group. In spite of the significant increase of serum vitamin B_{12} levels in aged subjects after oral administration, there were no observed differences in weight gain, appetite, and sense of well-being during the study. Future studies are planned to include the <u>in vitro</u> assay of serum antibody to intrinsic factor, Vitamin B_{12} complex of subjects with very low vitamin levels and the evaluation of the metabolism of methylmalonic acid in the same population.

Study of Effects of Nutrition and Aging on Bacterial Cell Surface Sites Reactive to Nucleic Acids, Vitamin B_{12} Antibiotics, and Other Compounds

We have observed differences in the interaction of "resting" cells of certain lactobacilli (L. lactis dorner, L. leichmannii, ATCC 4797, and others) after aging in a non-metabolic environment with nucleic acids, polyamino acids, vitamin B_{12} and several antibiotics. Earlier, we also reported that highly polymerized nucleic acid preparations inhibited the microbial absorption of vitamin B_{12} tagged with $Cobalt^{60}$ for easy identification. Both RNA and DNA possess the capacity to desorb previously adsorbed microbial vitamin B_{12}. These observations indicate that nucleic acid competes with vitamin B_{12} for similar cell surface sites. Either the addition of nucleases to nucleic acid or the aging of bacterial cells neutralizes this property of nucleic acid. The extent of inhibition of vitamin B_{12} uptake by the "resting" cells of these microorganisms is proportionate to the quantity of the nucleic acid added. An assay for nucleic acids (RNA and DNA) can thus be achieved by this technique as well as for the nucleases which neutralize the inhibitory effect.

The objectives of this study are in part to investigate the changes that take place on the bacterial cell surface during aging which result in the neutralization of the inhibitory action of the nucleic acids. Second; to study the effect of the previous nutritional history on the aging of the bacterial cell surface reactive to vitamin B_{12}, certain antibiotics, nucleic acids, and other compounds. Third; to study the action of DNAase on DNA isolated from "young" and "old" cells by the techniques developed in our laboratory. Fourth; to determine whether any of these observations have clinical application.

"Resting" cells of lactobacilli and other microorganisms were aged similarly to the procedure described by Davis et al, and Blankenship and Doetsch in a nonmetabolic environment at different temperatures, 0, 25, and 32°C for varying periods. The standardized "resting" cells were then treated with nucleic acids, vitamin B_{12}, antibiotics and other substances before and after varying conditions of aging. In other experiments "resting" cells were grown in a media containing graded amounts of nucleic acids and the resultant harvested "resting" cells were then subjected to similar conditions as described above.

Freshly harvested cells (stationary phase) and cells aged for short periods of time were very sensitive to the inhibition of $Cobalt^{60}$ Vit.B_{12} uptake by small amounts of DNA and RNA. However, cells aged in buffer solutions slowly lost this sensitivity to nucleic acid inhibition, but not to the uptake of vitamin B_{12}. This acquired resistance of the aged cells to nucleic acid inhibition is very similar in certain respects to the properties of kanamycin and neomycin in the prevention of $Co^{60}B_{12}$ uptake. We have also

made some preliminary observations concerning the effect of nutritional background on the aging of these bacterial cells. We observed that the loss of sensitivity of the aging "resting" cell to certain antibiotics, polyamino acids, nucleic acids and other biologicals resembles the loss of sensitivity to these inhibitory compounds when bacteria are grown in media supplemented with increasing amounts of nucleic acid. Our observations indicate that the nutritional history and age of the microbial cells have an influence on the cell surface sites reactive to these compounds. Blankenship and Doetsch have reported that the exposure of "resting" cells of A. aerogenes to narcotics with resultant delaying of associated age changes such as in the case of lag time length. They assume this may be due to the absorption of small quantities of narcotics to cell surfaces which then could serve as stimulants when organisms are placed in growth media. In our studies, the adsorbed compounds may compete for cell surface sites combining with vitamin B_{12}. Several workers have demonstrated changes in enzymatic activities with aging of bacterial cells. The "aging resting" cell may produce nucleases to hydrolyze DNA, RNA, and/or other enzymes in response to various substrates. Such release of nucleases may account in part for the lack of sensitivity of the older cell to DNA inhibition. Other workers have shown age-associated changes in cellular chemical composition, morphology, and resistance to chemical agents.

It is interesting to note that "resting" cells at $4^{o}C$ for several days became refractive to the inhibition of vitamin B_{12} uptake by kanamycin. We plan to study whether DNA and RNA isolated from both young and old microbial as well as animal cells are different in their inhibitory properties and their sensitivity to DNAase and RNAase hydrolysis by use of a radioisotope-microbial assay technique. We also plan to study the cell surface changes of bacteria grown with supplemental nucleic acids as well as aging bacterial cells since they exhibit several similar properties. We plan to explore further why DNAase at low concentrations increases rather than decreases microbial absorption of vitamin B_{12} in the presence of a small amount of DNA. We plan to quantitate cell surface components by techniques established in our laboratory to relate, if possible, aging changes with chemical composition.

Serum Enzyme Studies of Different Aging Populations

We have been concerned during the past several years with changes of serum enzymes during the aging process of different institutionalized and noninstitutionalized populations. Such studies may be of value in serving as a systematic approach to the establishment of normal biologic values for different aging populations, in the evaluation of the impact of pathology on these levels, and in the understanding of the influence of one biologic value on another. Fasting venous blood samples were drawn from subjects between the ages of 18 to over 90 years. All subjects

were ambulatory and free from acute disease with the exception of one group, namely, the Intermediate Service (IS) patients. After clotting, serum was separated and an aliquot frozen at minus 20°C until analyzed. Several enzyme determinations were performed on fresh serum. Other determinations were sent or delivered frozen to Dr. Charles H. Barrows, Jr., NICHD, Baltimore City Hospitals, for analysis of selected enzymes. These serum enzyme analyses were performed on: (1) VA Domiciliary Service (DS) members, presumably representing subjects maintaining normal physiologic funtion with no overt obvious diseases; (2) IS patients representing subjects in decline with identifiable chronic and acute diseases; (3) noninstitutionalized populations carefully screened (heat tolerance) subjects, Spanish American War veterans, college students, and controls. Our studies indicate that certain serum enzyme activity patterns change with age and may be dissimilar in different aging populations, for example, serum cholinesterase levels of both the DS and IS subjects decline with age. The serum cholinesterase regression pattern of a population of 150 noninstitutionalized subjects was very similar to that of the DS. The IS population exhibited significantly marked agewise decrement. The difference in this agewise regression between the IS and DS population was significant at the 0.001 level. In collaboration with Dr. Barrows, we observed an agewise positive regression of serum DNAase level with age ($P<0.001$). Serum RNAase levels of the IS patients were higher at every aging decade reflecting additional pathology. We also observed regressions in serum SGPT activity in both populations. In all enzyme systems studied, the agewise serum patterns of the DS and noninstitutionalized subjects were very similar. Of the serum assayed, two failed to show any agewise differences among the "healthy" members of the population. With three other enzymes the age changes over the last five decades, although statistically significant ($P<0.001$), were only in the order of 15%.

Thus, we do not see marked changes in enzymatic activities in serum of populations with minimal pathology. Our data do not offer strong evidence that enzymatic activities in human serum are markedly affected by aging.

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Gerontological Research in Social Work Service

The main thrust of the gerontological research program at this station is toward the identification and examination of social correlates of the aging process and the effects of aging on the provision of medical and social work services.

A recent study, the final report of which is being completed, investigated the social adjustment, health, medical and social work treatment, history, socioeconomic status, and attitudes of nearly 800 Spanish American War veterans. Currently, a 5-year follow-up of the original study subjects is underway. Its objectives are to ascertain changes over this period on selected social functioning, health, socioeconomic, living arrangements variables and to determine what factors are most clearly associated with longevity.

The final report is being written on a three station social work service study which examines the social work process from the points of view of the practitioner and the client. Age related differences in perceptions of referral source, presenting problem, prior management of problem, service requested, service expected, treatment goals, frequency of practitioner/client contacts, severity of problem, and outcome of social work service intervention will be analyzed. This study is concerned with such questions as: What is the effect of the aging process upon the practitioner/client relationship? How valid is the notion that the older a person becomes, the more he resists or avoids change, the harder he is to reach therapeutically, and the more superficial becomes the helping relationship.

Another study is concerned with psychosocial factors associated with "sick role" variations and response to social work service of medical outpatients. This study of patients who have failed to assume the modal patient role, explores the relationship between the two role variations and utilization of social work service, biographical, clinical, social functioning and attitudinal factors. This investigation will endeavor to assess the influence of aging on the maintenance of these atypical patterns of response to illness.

This worker is acting as consultant on two gerontologically-oriented studies. The first is an exploratory study by a Bay Pines VA Center Social Worker, of geriatric patients placed in contract nursing homes. This project seeks to determine the association between placement outcome and other variables. The second investigation, undertaken by the Outpatient Clinic team, is concerned with factors influencing the adherence of ulcer patients to a medical regimem. Variables to be considered are: knowledge of the disease and diet prescribed, age, marital status, occupation, education level, duration of illness, and length of treatment at clinic.

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Prophylactic Psychopharmacology and Age-correlated Intellectual Changes

Most pharmacological efforts are remedial in nature, i.e., oriented toward healing or improving a defect. In the case of aging per se, there is nothing obvious to heal. To be sure, deficits and performance reductions appear to occur with increasing frequency as one ages, but what to correct is not clear. Prophylactic pharmacology is another matter. Drugs to maintain performance in spite of the aging process are certainly feasible

Three general approaches have germinated in recent years. All are founded on promising hypotheses and all deserve more attention.

Consider, first, maintaining the nutrition of the nervous system. It has been estimated that an average of 10,000 nerve cells per day die and are irreparably lost to the human. This is, of course, an average; the loss is much greater in older years than youth. While the nutrition of the nervous system is a complicated matter, an obvious candidate for study is the oxygen uptake of the neurons. Progress is also being made in pharmaceutical intervention to maintain systematically healthy arterial walls. Although this effort is oriented primarily against sclerotic processes, it certainaly also holds relevance for neural nutrition. Finally, Cameron appears to have demonstrated that supplementing neural RNA with yeast-derived RNA is beneficial for intellectual performance.

Another tack, related to but operationally different from the nutritional approach, is that of (hypothesized) stimulation of the production of RNA within the nerve cell by means of an effectively non-nutritive agent.

In addition to the nutritional, or quasi-nutritional approaches, many substances exist now for mood and motivational control. With the increase in alertness and motivational level produced by such substances, many of the deficit areas may be obscured or rendered trivial; i.e., there is some merit to the Hullian theory of performance being a multiplicative result of drive and ability. The chronic administration of many of these agents is safe and perhaps beneficial.

All three approaches offer interesting hypotheses. It will be a long time until selection (if any should ever be done) will be

made among the approaches. Rather, intensive research should be done on all. As the relationships between behavior, on one hand, and anatomy and physiology, on the other hand, are little understood, the research field is a difficult one.

Aside from the complexity of relationships which may actually exist between these classes of variables, the main sources of difficulty lie in the unreliability of their measurements. The coefficient of attenuation makes this explicit; to the extent that the reliabilities are anything short of perfect, the observed relationship will be attenuated from the "real" relationship. Pharmacological research has been plagued traditionally by three really unnecessary, sources of unreliability--between observer variance, between epoch variance, and between culture variance. A solution to this situation seems to have been developed in this laboratory.

Totally Automated Psychological Assessment Consoles (TAPAC) which are pre-programmed devices with which the patient interacts in a self-paced manner have been developed. Currently measurable are reading and hearing comprehension, general intelligence, ability to learn (both facts and concepts), memory for both aural and visual events, aural and visual time perception, reaction time, decision time, and psychomotor ability. The test retest reliabilities of these measures are continually being improved, but now average in the high seventies, which is adequate for research purposes. Because the consoles are calibrated, between epoch and between examiner variance is negligible.

The present effort represents a series of experiments, each a double-blind double crossover procedure, evaluating the effects of an (hypothesized) prophylactic psychopharmacological agent against a placebo. Essentially healthy men, over 50 years but less than 70 years of age, participate as volunteer subjects. Typically, they remain on each medication for about six weeks, being evaluated on TAPAC at each cross-over.

The research is inherently long-term in nature. The aging process cannot be hurried, and, for a drug to have minimal side-effects when chronically administered, its primary action probably has to be subtle. Further, because of the enormous between-individual variance in such a sample of subjects, large samples are demanded to reach decisions. For these reasons no positive results of the effort are even anticipated for several years. Its automated character will allow it to run routinely, evaluating promising agents until an effective one is found.

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Immunization to Influenza, Diphtheria and Tetanus, Duration and Intensity of Protection

This project was to include a study of the value of immunization in diphtheria, tetanus and influenza in a geriatric setting. It also intended to study the various methods of immunizing, such as intradermal, subcutaneous and jet gun.

The program utilized mass immunization with blood studies to determine the extent and degree of immunization produced. The majority are in the age group of 60 or above. A program for protection in the aging and chronically ill patient will be proposed upon completion of this study. Specific goals to be achieved are: 1) to determine the feasibility of administering an immunization program to an aging population and to a group with chronic disease; 2) to determine the extent of immunity produced by various routes of administering an antigen; 3) to propose an immunization program for inclusion in a preventive medicine program for a Domiciliary or for a group with a fairly constant population; 4) to determine if possible the protection and duration of protection afforded the vaccinated individual against influenza during an epidemic.

Progress: The program has immunized several thousand individuals and has apparently given protection to those immunized during recent epidemics.

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Aspects of the Radioisotope-Hematology Research Program as it Relates to Aging

As part of the study of the biologic significance of vitamin B_{12}, studies of the serum level of this vitamin were done in the aged population. The basis for this evaluation relates to the evidence in one paper from England that beyond the age of 60 years the mean serum B_{12} level is lower than in those younger than 60 and, in addition, a further decline was suggested with each successive decade. An ancillary, better established observation is that peripheral nerve degeneration classically occurs with aging. Thus, well defined neurologic deficit, as identified by loss of positional and vibratory sense in the lower extremities, is noted clinically in advancing years. Histopathologic studies have documented that demyelination of nerves occurs with aging. Since vitamin B_{12} has a critical bearing on the integrity of neural

tissue, the relationship of the serum level of vitamin B_{12} and peripheral nerve function is under investigation. Preliminary observations suggest that any significant alteration (lowering) of the serum vitamin B_{12} level in the aged relates to dietary inadequacy over a prolonged period and not to any intrinsic abnormality in the metabolism of vitamin B_{12}. Since absorption of vitamin B_{12} depends upon secretion of intrinsic factor from the stomach and since achlorhydria has also been noted in the aged, this may be an additional mechanism limiting the absorption of vitamin B_{12} in already inadequate diets. That this is a minor added feature has now been demonstrated in that many of the aged patients with fasting achlorhydria do produce significant gastric secretions with histamine stimulation.

Current studies are now being directed toward the mechanism of action of vitamin B_{12} in neural function regardless of the age of the patient. Preliminary data suggest that, in vitamin B_{12} deficiency, abnormal lipids are formed which may affect the integrity of the normal lipid-laden nerve sheaths resulting in abnormal neural function.

In the ongoing studies related to iron metabolism, we have begun investigating the gastric factors which are important in iron absorption. It has long been recognized that gastric atrophy and achlorhydria are common findings in the aged. In addition, Herbert and his colleagues have noted that patients with pernicious anemia who, as part of this disease entity have gastric atrophy and achlorhydria, have a defect in iron absorption. This defect can be corrected by the administration of normal gastric juice, suggesting that some gastric secretory factor, necessary for optimal iron absorption, is absent from gastric juice from patients with gastric atrophy and achlorhydria. We have been engaged in studies relating to iron absorption in the presence of gastric juice from several sources, including achlorhydria and attempting to biochemically identify the pertinent factor or factors. Due to the preliminary nature of the results so far obtained, no definite conclusions can presently be drawn. It can be said, however, that if the absence of such a factor is found in association with gastric atrophy and achlorhydria, then it is possible that significant impairment of optimal iron absorption may occur in a sizeable proportion of the aged population.

Finally, studies are in progress concerning the relationship of platelet lipids to the formation of atherosclerotic plaques in the aorta. One of the classic theoretical mechanisms for atherosclerosis is the transfer of lipids from the cellular elements of the blood into the aortic wall. Recently, Mustard in Canada has reported that such transfer of platelet material may occur and he postulated this as the basis for significant lipid deposition in

the aortic wall. Since chronic depletion of platelets is possible, a study of the formation of atheromata in rabbits is in progress. Preliminary data suggest that the induction of a severe and chronic thrombocytopenic state does not alter the rate or degree of developing atherosclerotic plaques.

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The Regulation of Intracellular Protein Metabolism During Development

Few fundamental investigations attempting to separate and contrast the anabolic and catabolic components of the "dynamic equilibrium" of proteins which theoretically plays a role in growth, maturation, and aging, have appeared in the literature. Although literally hundreds of studies reporting age-related changes in levels of activity of numerous enzymes in various tissues have been published, the rate of turnover or renewal of this vital cellular machinery and its functional capacity as delimited by substrate availability has been largely ignored from the gerontological standpoint. The rationale of the approach described herein is not so much to determine the significance to aging of the rates of synthesis and degradation of any certain enzyme or enzyme system, but the capabilities and limitations of aging cells for autorenewal with respect to proteins both structural and functional and, in the latter case, the efficiency with which they function.

The phenomena of enzyme induction and disappearance and enzyme depletion and repletion represent unique approaches to the study of protein metabolic balance in the sense discussed above. We have already shown that the kinetics of accumulation of tryptophan pyrrolase in rat liver in response to tryptophan administration undergoes a transition during growth and maturation. This differential response can be interpreted as a shift in the balance of anabolic and catabolic processes associated with intracellular protein metabolism or a change in the conditions or mechanism of accumulation of this enzyme. In the latter case we have shown that the observed age-related alteration is not the result of changes in the pattern of tryptophan uptake with age. Recently we reported that the rate at which the tryptophan "induced" enzyme returned to its basal level varied with age in the order: 12- month old $>$ 6-month old $>$ 1- month old. In an attempt to delineate the catabolic contribution to these decay curves from the on-going synthetic process, we have now discovered what may be further correlation between development and enzyme "induction". From all outward

apperances, male Fischer 344 rats are less well-developed at one month of age than are Holtzman (Sprague-Dawley) rats. We find that the initial rate of accumulation of tryptophan pyrrolase, in response to tryptophan, is 2- to 3- fold greater in 1- month old Fischer rats than in 1- month old Holtzman rats. While this may simply be a strain difference, we are currently studying the response of the enzyme to tryptophan administration in Fischer rats from birth to three months of age. Although other workers have reported on the "induction" of tryptophan pyrrolase in the pre- and post-natal periods, they did not correctly assess the situation inasmuch as they measured the enzyme level only at 5-6 hours after tryptophan injection. During this time the enzyme "waxes and wanes" in very young animals, as we have already shown. Future studies on enzyme induction as a function of age will be concerned with the response of several inducible enzymes to hydrocortisone administration.

The initial phase of our work on enzyme depletion and repletion (with xanthine oxidase as the model) is nearing completion. Preliminary indications are that age-related differences do exist although no clues to the cause of such differences have been turned up. In vitro depletion studies using tissue slices will be made in search of such clues. An outgrowth of this study has been the discovery that the fluorometric assay of Lowry et al. for xanthine oxidase is not valid when applied to crude tissue extracts. We have reported this finding together with modifications which validate the assay.

As a part of these and other studies a rather ambitious project to qualitatively and quantitatively characterize the intracellular free amino acid pools of various tissues during aging will be inaugurated. We also plan to study the effect of derepression upon the susceptibility of specific genomes to irradiation.

Another project currently underway in this program is the study of local blood flow in various tissues and organs of rats as a function of age. While at first sight this may appear to be a totally unrelated project, it is reasonable to assume that intracellular metabolism may be affected by age-related changes in the rate of blood flow. Not only will the supply of oxygen, substrates, and hormones for energy production, anabolic processes, and metabolic control be altered, but also the removal of toxic wastes or potential metabolic "clinkers" will be affected. Therefore, any studies in vivo aimed at discovering differences in the functional (metabolic) efficiency of young and old cells will be well served by a knowledge of the limitations imposed upon them by circulatory changes with age. In this connection we have succeeded in our efforts to modify the hydrogen clearance method of Aukland et al. so as to be able to measure local cerebral blood flow in unanesthetized, unrestrained animals. The only other

method available for such chronic measurements is the heat clearance technique which is far more complex and/or only measures relative blood flow. We are now in the process of measuring local blood flow in various parts of the brains of conscious rats at different ages. We also plan to determine whether there are any age-related differences in response of local cerebral flood flow to chronic hypoxia, hypercapnia, and various drugs known or suspected of affecting cerebral circulation.

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Iodine in Serum
I. Qualitative and Quantitative Appraisal
II. Changes with Age and Thyroid Status

Description of Research: The work, which occupied most of the time during the past two years, had been initiated in 1962 on occasion of a request by Dr. McGavack for protein bound (PBI) and total iodine determinations on sera of certain patients of his who had unusually low iodine uptakes but were clinically euthyroid. This finding Dr. McGavack considered of particular interest as it occurred in individuals in whom it may have been a consequence of a metabolic adjustment to aging. The use of the then well established ceric sulphate reduction tests for iodine met with unforeseen difficulties caused both by inhibition of the reaction and by substances that reduce ceric sulphate non-catalytically and simulate iodine. After many attempts to eliminate such interference with the aid of information obtained from the different characteristics of the ceric sulphate fading curve, it was decided that a safe analysis is possible only if all organic material is eliminated prior to the fading test. The discovery that the concentration of perchloric acid in the residue after ashing markedly affects the sensitivity led to a greatly improved reproducibility, of $\pm$ 0.35 ng iodine per test sample (Clin. Chem. 10:799-823, 1964). This method was used in the simultaneous study of thyroid, gonadal, and adrenal function in aging men (J. Geront. 20:383-393, 1965). The method had been further improved in connection with subsequent work which provided evidence for small molecular weight T_4-binding material (Biochem. 4:931-939, 1965). This material was considered to have importance as regulator for the level of non-protein bound thyroxine. Sterling and Brenner (J. Clin. Invest. 45:153, 1966) point out that, "if the findings of Hoch and co-workers are corroborated, it would appear preferable to regard the thyroxine in dialyzates and ultrafiltrates as 'non-protein bound', 'diffusible', or 'dialyzable' hormone, since it may not be present in solution as a free anion, but could be partly bound by a diffusible small molecule. Such a concept is by no means unreasonable in light of present information concerning thyroxine interactions. Pending further clarification of the

physical chemical state of thyroxine in dialyzates, the so-called 'free' thyroxine should be understood to indicate the nonprotein bound moiety."

The phenomenon that dilution of serum with phosphate buffer results in a rise in unbound thyroxine fraction only about half as great as might be anticipated a priori might be explained by the presence of dialyzable thyroxine binding substances which, on dilution, might have only negligible binding effect on thyroxine.

It is well established that at least 4 serum proteins ordinarily bind more than 99.9% of the circulating thyroxine. The level of free, non-protein bound thyroxine in serum is a measure of the metabolically available hormone, and this level can be determined with the aid of radioactive T_4, but not chemically. Recent improvements in the chemical determination of iodine extending the range down to 0.01 ng iodine per sample (publication in preparation), now appear to make possible the measurement of dialyzable T_4 in serum also by chemical means. PBI determinations on 7 sera done in duplicate on 12 µl by this new micro method were compared with those done on 0.1 ml serum by the dry ashing method (Bioscience Laboratories). The two methods agreed satisfactorily; but the dry ashing method tended to give results lower by 0.2 to 0.3 µg/100 ml.

A paper chromatographic method for semiquantitatively determining dialyzable thyroxine binding material (Biochem. 4:931-939, 1965) has been used to study sera from patients and staff members as related to age and iodine uptake (unpublished). In view of the possibility of measuring the direct effect of the dialyzable thyroxine binding material on the level of free T_4, work on the binding factor with the more tedious chromatographic method was temporarily interrupted.

Dr. Roman T. Markiw, who has recently begun work in the Physical Chemistry Laboratory, will study peptides in urine as related to age. After purification, these peptides will be analyzed for iodine content.

As has been noted above, our earlier work was concerned with obtaining serum iodine data for aging subjects. During these experiments a low molecular weight thyroxine-binding material was discovered in dialysates of serum. The methods developed appear promising for a study of alterations of this thyroxine-binding material as a function of age.

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Gastric Secretory Capacity in the Normal Aging Population
Gastric Secretory Function in New Duodenal Ulcer Patients Over 50

Data concerning gastric secretion in older age groups is incomplete. Furthermore, available information does not specifically concentrate on the population over 60 years of age nor is it based on reliable and reproducible methods of gastric analysis.

Establishment of accurate data concerning the gastric secretory function in older age groups requires large population samples in various age brackets. Because of this, and the known difference of sexes, a cooperative study between the VA Hospital and Milwaukee County Hospital was formulated three years ago. Both population groups are being studied in standardized gastric secretory laboratories in each hospital. The patients are being tested by the Augmented Histamine Gastric Analysis, which is recognized as the most accurate and reproducible test of gastric secretory function.

The following is the number of patients and their respective age categories who have had gastric secretory studies at the VA Hospital up until October of 1967. Data are not yet compiled at Milwaukee County Hospital.

Age Category	Patient Number
40-50 years	102
50-60 years	50
60-70 years	42
70-80 years	44
80-90 years	1

The older patient is thought to have a diminished gastric secretory capacity, yet patients over 50 years are frequently noted to develop duodenal ulcers. Some authorities feel that this disease is unlikely in a patient over 30 years of age if the maximum acid output, following an augmented histamine test, is less than 11mEq per hour. There would seem, therefore, to be a threshold figure for acid secretory values below which duodenal ulcer is unlikely to be found. No study has tested this assumption in older patients, nor do we know whether the etiological association of "high acid-duodenal ulcer" normally found at younger age levels is applicable to the older patient.

We have studied the gastric secretory range in 12 patients with de novo duodenal ulcers occurring after 50 years of age and are in the process of collecting more patients for this group for comparison with a normal control population.

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Developmental Biology of Aging

I. Cellular Interactions in Relation to Aging.--This approach to the etiology and pathogenesis of conditions in the aged organism is concerned with deficiencies in the orderly relationship of cells to one another. Attention is directed particularly toward the relation of immunologically competent cells to other somatic cells. The immunologically competent cells normally possess the ability to distinguish between bodily components and foreign or "non-self" materials, and to react against the latter. The immunological system may function in part, as Burnet (1961) has suggested, to police aberrant cells that arise in the body as a result of somatic mutation. It is conceivable, then, that somatic mutations among the immune cells might lead to an increasing tolerance of foreign antigens and aberrant cells, permitting a greater diversification among somatic cells, to the detriment of orderly functioning of entire systems of cells. Alternatively, as Walford (1964) has suggested, diversification among immunocytes could permit some of them to recognize normal cells as foreign, and thus to react against them, in the manner of a chronic, low-grade graft-versus-host reaction across weak histocompatibility barriers. A similar mechanism has been implicated (Tyler, 1960) in the pathogenesis of cancer, a disease that is more prevalent among the aged. The cancer theory of Albert Tyler proposes that the initiating event in carcinogenesis is the loss or inactivation, through the action of ionizing radiation, a virus, or a chemical carcinogen, of a histocompatibility gene in a normal cell. This event is followed by the loss from the cell surface of the corresponding histocompatibility antigen. It is postulated that the altered cell then recognizes the surrounding normal cells as foreign to itself and proceeds to react by proliferating and forming immunologically active products.

Two types of tissue-culture experiment are being employed in this laboratory to explore problems of cellular interaction. The first of these was designed to demonstrate the relation between the proliferative response of lymphoid cells and the strength of the isoantigenic stimuli to which they are experimentally exposed. The initial experiments showed that in tissue cultures containing

a mixture of spleen cells from two congenic strains of mice differing at the H-2 locus, the proliferative activity of the cells (indicated by incorporation of tritiated thymidine) was significantly increased over control levels. Increased proliferative activity was also found in mixtures of normal splenic cells with mitomycin-C-treated (mitotically inactivated) splenic cells of a foreign strain, but not in mixtures of normal cells with foreign cells killed by freezing and thawing. The mixed-culture technique permitted a distinction between homozygous and hemizygous dose of foreign H-2 antigens, but did not reveal any significant difference between unidirectional responses in reciprocal combinations of two strains, nor between unidirectional responses of parent strain against F_1 hybrid and F_1 against parent. The initial findings suggested that non-immunological factors, such as cellular injury or humoral mitogenic agents, can contribute to the responses observed in mixed lymphoid-cell cultures. A humoral mitogenic factor, possibly identical with histocompatibility antigens, had previously been reported in mixed cultures of human leukocytes (Kasakura and Lowenstein, 1965). Because of the potential applicability of mixed leukocyte cultures to human tissue-matching, and because of the theoretical importance of defining precisely the nature of the proliferative stimuli to the lymphoid cells, further experiments are being conducted with this system. In some of these, cellular fractions containing serologically active histocompatibility isoantigens are added to cultures of splenic cells; in others, the culture medium is removed from cultures of growing cells and added to fresh cell cultures in order to test for mitogenic agents released by the growing cells.

A second type of in vitro experiment is designed to explore contact-inhibition phenomena, and to test the hypothesis that loss of contact inhibition in cultures can be a consequence of interaction between antigenically dissimilar cells. In these experiments cultures of embryonic mouse fibroblasts that exhibit contact inhibition are augmented by the addition of adult splenic cells from the same strain of mouse or from a foreign strain. Enumeration is made of areas in each culture in which contact inhibition of cellular growth is lacking. In later phases of this project, embryonic cells of two inbred strains of mice and their F_1 hybrid will be cultured alone or in various combinations, and the available procedures for evaluating contact inhibition will be compared.

II. Mitochondrial DNA in Relation to Aging.--Senescence may be defined as the decline in various functional capacities with advancing age. The decrease in some capacities can be related to losses of cells; other declines seem the result of impaired cellular functioning which, in the view of some authorities, may be related to intracellular losses of mitochondrial units. Recently several investigators have characterized the molecules of DNA that are associated with mitochondria in animal cells, and Dr. L. Piko

of the Developmental Biology I Laboratory at this station has, along with his associates at the California Institute of Technology, related the number of mitochondria per cell to the number of uniformly sized, circular, mitochondrial DNA molecules in the cell (Piko, Tyler and Vinograd, 1967). If, as seems likely, it is generally true that each mitochondrion in a cell is associated with one (or at the most two) circles of DNA, then it becomes possible to count mitochondria by measuring DNA, and to compare mitonchondrial numbers in old cells with those in young cells. Preliminary studies are in progress to determine the best methods for isolating and analyzing mitochondrial DNA from mammalian tissues. A series of experiments is planned in which brain, heart and other tissues from laboratory mice will be analyzed for their content of mitochondrial DNA, and comparisons will be made among the tissues of animals of various ages. Further experiments will be concerned with mitochondrial DNA in certain disease states and in normal development; other matters, such as the replicative potential of mitochondria, and the possibility that the circular mitochondrial-DNA molecules might be infectious, will also be investigated.

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Gerontological Psychology Research

There is little doubt that learning performance declines with increasing age (Botwinick, 1967). One of the central problems in the psychology of aging is whether the observed age decrements in learning performance are due to age changes in the capacity to learn, or to age changes in non-learning factors such as motivation, loss of speed of response, or health. Although it is difficult to separate the contributions of learning capacity and non-learning factors to age-changes in learning performance, such a separation is necessary in order to elucidate the learning changes which occur in later life, and the psychophysiological factors that may underlie these changes. If it can be established that there are no age changes in the non-learning factors, then the observed changes in performance may be attributed to age changes in the capacity to learn. Presently there are relatively few studies that test the notion that non-learning factors rather than learning capacity produce performance deficits with age (Botwinick, 1967).

If older organisms are slower on some learning tasks, could this be due to lesser motivation? The obvious procedure of depriving animals of food or water for equal time and then examining their learning performance under such deprivations does not yield a clear-cut answer. It is not known whether young and old rats, starved for the same time, are equally hungry or equally motivated (Kay, 1959).

Little research has been done on the effects of age on motivational states per se, e.g., hunger, thirst, sex, etc. This is surprising in view of the central position held by the concept of drive in behavior theory. Jerome (1959), in his extensive review of the experimental studies in age and learning concluded that progress in the understanding of the relationship between learning ability and age is predicated upon considerable prior clarification of the relationship of both of these factors to motivation. Although the motivation-learning relation can be safely left to the general experimental psychologist, gerontological psychologists will have to accept the responsibility for investigating the age-motivation relationship.

In view of these considerations, the aims of the Gerontological Psychology Research Laboratory program at this time are:

1) To describe the age-related changes, if any, in the effects of drive conditions on the energization of behavior as measured by general activity, consummatory behavior and the performance of learned instrumental acts. The drive conditions to be studied include food deprivation, water deprivation, and electric shock.

2) To explore various methods of specifying drive conditions so that its effects on the energization of behavior are comparable across different age groups of animals.

3) To relate the observed age changes in drive to alterations in physiological variables as a function of age.

The first experiments had established that there were age differences in the effects of a given duration of food deprivation on drive as measured by increases in wheel-running activity. These experiments further established that percentage of body weight loss was a more comparable way of specifying the degree of need and drive in rats of different ages than duration of food deprivation. The results of a subsequent experiment using the consummatory response as the dependent variable, indicated that the two ways of specifying the antecedent condition of drive, viz. hours of deprivation and the percentage of weight loss, are equivalent when comparisons are made among age groups of rats that are similar in growth rate. The two modes of specifying the antecedent conditions of drive give discrepant results only when growing rats are compared with non-growing rats.

A subsequent study determined that the age differences in survival time in the original experiment were partly due to age differences in the rate of running in response to food deprivation. Since the younger rats manifested higher rates of running activity in response to food deprivation than older rats, they used up their stores of energy at a faster rate, and died sooner.

Experiments such as these are elucidating the mechanisms underlying age-related changes in motivation in rats, and are providing needed background information for future investigation of the physiological bases of age-related changes in motivation.

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Effect of Analog-Substituted RNA's on Protein Synthesis

My colleagues and I are studying the effects of certain agents which interfere with the formation of RNA in the brain of experimental animals. These agents cause damage to nerve cells which in certain respects resembles that seen in brains of senile human subjects. We feel that these studies may shed light on some of the changes in cell chemistry which contribute to premature and normal aging of brain cells in man.

Studies of Neural Lysosomes

Another relevant aspect of our work is the accumulation of age pigment in brain cells of elderly subjects. Age pigment seems to represent the indigestible residue which results from intracellular digestive processes. Excessive formation and accumulation of age pigment in brain cells represents a kind of cell "constipation" which may interfere with normal brain function. We are investigating the chemical composition and mode of formation of age pigment, and of lysosomes, which are closely related to the former, in the brain of experimental animals. Lysosomes are intracellular particles in which are stored a number of potentially destructive enzymes. Age pigment also contains these enzymes. Deeper knowledge of the processes leading to the production of these cell materials should extend our understanding of the aging process in brain and perhaps give clues to its modification.

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Effects of Aging and Hormones on Pyrimidine Utilization for Nucleic Acid Synthesis

It is well established that metabolism in animals and animal organs declines with the aging process. It also must be postulated that an imbalance between the rates of anabolic and catabolic processes develops during aging, in which catabolism predominates, and results in a decrease in the efficiency of mechanisms for the reconstitution of essential structural and functional cell components. This refers primarily to altered ability to metabolize proteins which

may be directly related to an alteration in the ability of the cells of the aged animal to form nucleic acids. It is well established that the content of free nucleotides, especially ATP, decreases markedly with age and that the activities of some enzymes involved in nucleic acid synthesis may vary with age or growth rate.

It has been shown by Skold (Biochim et Biophy Acta 44, 1:1960) that there is a correlation in some cases between the activities of uridine phosphorylase and uridine kinase and the growth rate of the tissue examined. Regenerating rat liver exhibited an increase in activities of both enzymes, with a decrease nearly to the initial level 44 hours after partial hepatectomy. Furthermore, it has been shown by Stevens and Stocken (Biochem. J. 87, 12:1963) that uridine phosphorylase increases slightly in regenerating rat liver on the basis of the supernatant protein content but changes very little on the basis of DNA content. It was demonstrated, however, that a strikingly higher uridine phosphorylase activity was present in young adult rats as compared to fetal and newborn animals.

The purpose of this project is to study the effects of aging and of hormones on various aspects of nucleotide and nucleic acid metabolism. The effects of aging on the cell content of nucleotides, on the activities of enzyme in the pyrimidine pathways and on the utilization of preformed pyrimidines for nucleotide and RNA formation are being examined.

The free nucleotides (acid-soluble nucleotides) are separated by column chromatography and quantitated on the basis of UV absorption. The enzymes are assayed and studied either in extracts from various tissues or in tissue slices. Incorporation of radioactive precursors into nucleotides and RNA is investigated after injection into intact animals or incubation of tissue slices in a balanced salt solution. Pyrimidines, pyrimidine nucleosides and nucleotides are separated by column chromatography and RNA is prepared, hydrolyzed and quantitated by the spectro-photometric method of Munro. Radioactivity in various aliquots is determined in a liquid scintillation counter.

As a result of preliminary experiments, several interesting observations have been made. The activity of the enzyme uridine phosphorylase in the livers of old rats and adult cows is only about 10% as high as in young rats or in calves. Uridine kinase activity does not appear to be altered under these conditions. The possible alteration of other enzymes in the pyrimidine pathways with age is being investigated.

In contrast to the decrease in liver, the activity of uridine phosphorylase in the thyroid gland was not altered with age. However, under conditions of thyroid gland stimulation (thiouracil feeding) attributed to TSH, uridine phosphorylase and uridine kinase activities

increased by more than 100%. In addition, TSH has been found to stimulate pyrimidine nucleotide and RNA synthesis in slices of thyroid tissue. These results, which are by no means complete or extensive, suggest that the activity of some enzymes participating in nucleic acid synthesis decreases with age in addition to a decrease in cell nucleotides and that at least one hormone stimulates the activity of some of these enzymes in its target organ. The ultimate goal of this investigation is to determine if the decreases in uridine phosphorylase activity, and possibly other enzymes in these pathways, as well as the decrease in tissue nucleotides with age is associated with a general decrease in the ability to synthesize RNA. In addition, a possible reversal of these aging effects with various hormones, especially thyroxine which increase cellular RNA, will be investigated. This study should provide important information concerning the biochemical process of aging.

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The Effect of Surgical Trauma on Renal Excretion of Calcium, Magnesium and Zinc

Plasma and red blood cell zinc levels were determined on 206 normal males (age 18 to 86 years) and 58 normal females (age 20 to 80 years). There was a statistically significant fall in plasma zinc levels with age ($p < .001$) but red cell zinc levels rose in both male and female subjects with age. The latter was not significant ($p < .1$; $p \geq .05$), however. These data are being used to correlate these levels in normal persons with those having various forms of pathology.

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Nursing Home Studies

a. Factors Related to Nursing Home Effectiveness:

(1) Significance of Work: The primary goal of the nursing home has been defined as "maintaining and restoring patients to the highest possible level of health." Little has been done to single out particular characteristics of homes where this goal is likely to be achieved. With the increasing number of older chronically ill patients treated in the VA, the nursing home is a resource that can not be neglected. VA has a responsibility to its patients, in terms of extended care, and to the medical community in helping to raise the level of care provided in these homes. Nursing homes are growing in size and number.

The only way to help them grow in the right direction is to find factors related to effective care. The most impressive research to date has been by Stotsky and Goldfarb; however, this has been primarily in the area of nursing homes and mental health. The purpose of this study is to determine the influence on nursing home effectiveness of differences in physical facilities, staffing, administrative policies, and patient care activities. In each of 20 homes, chosen to provide variations in these regards, patients are studied immediately prior to placement and again 1 week and 6 months after placement. The fate of these patients will be the objective criterion by which effectiveness of homes will be judged.

(2) Method: Currently, we are about one-third through data collection with approximately 350 patients. Nursing homes are rated every 6 months on a Nursing Home Rating Scale. In addition, items such as size, staffing ratios and patterns, volunteer hours, cost, and turnover rates are computed. Data on patients include physicians' prognostic classification of improve, remain the same, or deteriorate and physician rating on a Cumulative Illness Rating Scale. Demographic, hospital, and medical information are collected. In addition, patient and family attitudes are also assessed. Hospital nurses provide baseline ratings on a Disability Scale and the same scale is re-rated by nursing home nurses 1 week and 6 months after placement. When approximately 50 patients per nursing home have completed their 6 months follow-up, a Multivariate Analysis of Variance (MANOVA) program, available through the Biometric Laboratory of the University of Miami, will be carried out between nursing home factors and patient outcomes (defined by physician's prognosis and differences between baseline and final ratings on the Disability Scale). This should yield factors related to effective nursing home care.

(3) Results: Analysis of data thus far has been only on characteristics of homes and patients separately. Only general impressions can be given concerning actual effectiveness. Factors which seem most likely to be related to effectiveness are: high staff-to-patient ratios, in-service training programs for staff, and homes with administrators who have some special training or orientation to geriatric problems. It is doubtful that actual physical facilities of the home will be significant. A review of data collected on 320 patients shows 45% have been predicted to improve, 30% to remain the same, and 25% to deteriorate. Death rate dropped from 34% the first year to 29% the second. Patients are about 67 years of age, with 65 hospital days, and an average of 2 previous hospitalizations. Their primary disorders are musculoskeletal, stroke, chronic brain syndrome, arterio-sclerotic heart disease, and diabetes. About 51% of the patients are married with 18% having no family listed as next of kin. The majority lived in their own home prior to hospitalization. About 89% had less than $200.00 per month income. About one-third of the patients expressed positive attitudes toward nursing home care, although 67% of the families expressed favorable attitudes. 267 patients have completed 6 months follow-up. Of these, 40% were still in the nursing home,

24% had been discharged home, 7% were back in the hospital (32% had been readmitted at some time), and 29% had expired.

(4) Future Direction: Consideration is being given to accepting a sample of male patients placed from the University Hospital. This has advantages of increasing patient numbers more rapidly and involves collaboration with and consultation to the Division of Continuing Care of the Medical School. Plans are also underway to survey a large sample of nursing homes across the country to determine by factor analytic methods the dimensions of nursing homes.

b. Collaborative Research with VACO Program Evaluation Staff:

Participation in data collection and currently, in the analysis of data on 845 patients placed in both community and VA nursing care units is underway. This has involved development of a diagnostic classification system and rating of diagnoses on all Ss. Participation in writing up results of this large multi-hospital study during the next year is planned.

c. Wives' Attitudes Toward Nursing Homes:

The Effectiveness Study is yielding data for independent but related studies in the area of nursing home care. One on-going study reported at the 1967 Gerontological Society Meeting concerns wives' attitudes toward nursing homes. 60 wives of aged male patients have been interviewed prior to their husbands' placement in nursing homes, and again 2 months after placement. Pre- and post attitudes are obtained. After 2 months experience with the homes, wives rate the nursing homes in terms of over-all care, staff, cleanliness, meals, physical facilities, and activities. Preliminary analysis reveals 57% of the sample had positive attitudes initially. After 2 months experience almost half were negative. Of the 26 who started negative, 8 changed to positive. Several step-wise regressions were used to predict attitude. The only significant predictor of pre-attitude was how long the patient was hospitalized. The longer, the more negative the initial attitude of the wife. 60% of the variance in final attitude could be accounted for by knowing how the wife rated the home on meals. The only significant items which added to the prediction carried by meals were ratings on overall care and activities. Data are still being collected with the intention of re-running the regression analysis at a later date on a larger sample.

d. Impairment & Disability as Predictors of Nursing Home Outcome:

Impairment is considered to cover diagnosis and extent of pathology and is traditionally rated by a physician. Disability refers to how impairment affects the persons in terms of functioning and incapacity. Although both are useful in assessing physical condition, one may be more effective than the other in predicting nursing home outcome. 267 patients were rated on a Disability Scale by hospital

nurses and on an Impairment Scale by physicians just prior to placement of these patients in nursing homes. Follow-up 6 months later provided several criteria for analysis. Each scale was first analysed by discriminant function between patients living and dead. Impairment predicted these outcomes at $P < .001$ while disability was $P < .01$. Multivariate analysis of variance between 4 outcome criteria of discharge, in nursing home, readmissions, and death again showed impairment a better predictor of these outcomes at beyond the .01 level. The same program run between criteria of improve, remain the same, deteriorated, and dead (with orthogonal polynomials requested to determine the curve of prediction) confirmed impairment a better predictor. At this time, write-up of data on this study is underway and future plans deal with construction of a new scale incorporating the items with the highest predictive value from each of these scales. A new sample of patients would be studied using the revised and combined scales.

e. Validity of Ratings from Medical Records:

It is often expedient to use medical records in lieu of personal contact with medical staff. There is usually a question regarding consistancy of records and validity of ratings. Sometimes medical records contain more than the staff is actually aware of in terms of history and other times personal knowledge exceeds that of recorded material. This study examines ratings on impairment of the patient as rated by the physician in charge of the case and also by other physicians using only the medical records. Ratings on a 13 item impairment scale are compared by product moment correlation.

f. The Myth of "Transplantation Shock" in Nursing Home Placement:

Comparison between the patient's condition in the hospital and one week after placement is being studied. Preliminary analysis, using discriminant function, on 230 patients does not support the generally accepted theory of "transplantation shock" in terms of the patients physical and mental adjustment.

Aging and Socio-Environmental Stress

This project holds that deteriorated functioning is related to environmental stresses. The way a person handles stress either increases or decreases his adaptive ability and proportionately contributes to the wear and tear of aging. This project would increase our knowledge of the effects of those coping patterns of behavior which would in turn provide a sounder base for our choice of treatment techniques for the aged. This research has been divided into several phases. Since adaptive and maladaptive reactions to stress probably begin in early childhood, the relationship of childhood stress to later social dysfunction was first considered. A preliminary step has also been the development of a scale to measure social dysfunction.

a. Development of Social Dysfunction Scale:

Development, testing, and refinement of this scale has involved a 3 year co-operative effort with the entire social work staff at Coral Gables, VAH. Opinions were first solicited from 50 VA Chief Social Workers regarding a definition of social functioning. From these a preliminary scale was devised. Community agencies were included in pre-testing the original scale which has undergone a series of revisions and modifications based on studies of reliability and validity. The present version contains 21 six-point scales covering areas of social dysfunction, based on subjective-objective evaluations of a person's activities and satisfactions. The item definitions draw heavily on concepts of Buhler, Kuhlen, Henry, Gordon, and Sullivan. Reliability was tested by 6 social workers independently rating 20 patients. A Kendall W = .91 was obtained between total scores. In addition 40 subjects living in the community were rated independently by 2 social workers and product-moment correlations between each item indicated reliabilities ranging from r = .68 to .89. Validity of the scale was assessed in a social work staff study in which functioning of 80 psychiatric and non-psychiatric outpatients was evaluated. Social workers, unfamiliar with the scale, made global estimates of the patient's adjustment and these correlated with total scale score at r = .89 (product moment). In addition, multivariate discriminant function analysis using IBM 7040 computer showed the scale discriminated these 2 groups at $p < .0001$. To determine factor dimensions useful in conceptualizing Social Dysfunction, principal Varimax rotation factor analysis was performed on ratings of 80 subjects. Five factors: Apathetic-Detachment, Dissatisfaction, Hostility, Health-Finance, and Manipulative-Dependency were identified.

b. Pediatric Correlates of Geriatric Adjustment:

The purpose of this investigation was to explore the relationship between early childhood experience and later adjustment, on the theory that there is a continuity of behavior. Aging, in this context, is seen as a dynamic process beginning at birth and continuing until death. From this point of view, the problems of old age have their roots in early development. One hundred V.A. outpatients, over age 65, were studied. Childhood characteristics such as number of siblings, birth order, cultural heritage, rural-urban environment, and socio-economic status were obtained. Childhood stresses such as death of parent, prolonged illness of parent or subject, emotional and physical deprivations or abuses were recorded. A social Dysfunctioning Rating Scale was used to measure the current level of functioning. Correlations between childhood items and later dysfunctioning were obtained. Subjects who had lived in rural environments during childhood had the least current dysfunctioning. Subjects from large families of native-born heritage also functioned better. A positive correlation existed between childhood stresses and later dysfunctioning, with death of a parent or prolonged illness of a

parent being most highly correlated. As might be expected the higher the number of stresses, the greater the degree of dysfunctioning. This project supports a developmental theory of aging and points to objectives of long range prevention, rather than merely the detection of existing problems of old age.

c. Future Direction:

An exploratory study of Aging: Psycho-Social and Biological Interactions is planned. Its purpose would be to identify changes in and between several measures of physical, emotional, and social functioning and to relate these to changes in the environment.

Physical Resistance in the Aged

It is poorly understood from a biological standpoint why some people become senescent at a relatively early age. It has long been recognized that chronologic age alone can not be relied upon as an index of aging. From the belief that persons must be born physically tough and endowed with a good body, the theory that longevity is related to past physical resistance is being explored.

(1) Instrumentation:

In order to measure the degree of organic pathology experienced by Ss in these studies, a Cumulative Illness Rating Scale (CIRS) was developed. The CIRS attempts to roughly measure biologic age in terms of cumulative pathology. The 13 item 5-point scales deal with degrees of impairment. Although many scales have been developed for rating disability, few have been designed for rating actual organ impairment. The CIRS has a Kendall's W = .92 for inter-rater reliability when tested independently by 6 physicians on the same 20 patients. Validity of the scale was assessed in a study on 472 geriatric patients in which significant correlations were obtained between high scale scores and outcome of death, high number of illnesses and vital organ involvement. The Scales most recent application has been in a VACO Program Evaluation study of 845 patients placed in nursing homes. Further validating information is currently being reported from its use by physicians in 18 hospitals in this study.

(2) Physical Resistance in the Aged-Part I:

Male Ss over 75 were compared with younger controls. Detailed health histories and physical examinations provided the basis for ratings of 172 Ss on the CIRS and for making diagnostic classifications. Hospital data and demographic information were also collected. Results showed us significant differences in the degree of pathology experienced by each of the 3 groups (ages 55-64, 65-74, and over 75) throughout their lifetime, indicating that the older Ss had been more resistive to illness. There were specific illnesses related to each of the age groups. The study suggested that persons with leading

killer diseases form a separate population from those who live into extreme old age. This phase of the research was reported in the Biological Section of the 19th Annual Gerontological Society Meeting in New York City in 1966 and forms the basis for the subsequent study of physical resistance and aging.

(3) Physical Resistance and Longevity:

The previous study was a comparison between living Ss and controls. The ultimate test of the relationship of past physical resistance to aging must of necessity use mortality as the outcome criterion. In this study, 300 Ss who died during a 2 year study period were placed in age groups of 55-64, 65-74, and over 75 for comparison. Ratings on the CIRS, diagnostic classifications, and demographic data provided 40 selected variables for multivariate analysis of variance on the IBM 7040 computer. There were no significant differences in total scores for the 3 age groups, indicating older Ss had lived longer with no greater degree of pathology than those who died in the younger age brackets. There were also no significant differences in number of previous hospitalizations or total number of past illnesses. Significantly more of the younger group had histories of cirrhosis, alcholism, injuries, and psychiatric disorders. At $P < .05$, more of the middle group had myocardial infarctions, bronchitis, and diabetes during their life. Histories of hernia and death from pulmonary embolism were the only two diagnostic factors related to the older group. Even though approximately 37% of each group had internal cancer, significantly more of the younger group had lung cancer and more of the older had genito-urinary cancers. Our study suggests that living into extreme old age may be less accidental survival and more biological eliteness with a special invulnerability to specific kinds of illnesses. Results of this study were presented in Nov. 1967 at the 20th Annual Gerontological Society Meeting and are reviewed in Viewpoint in Geriatrics (in press) and also in Feb. 15 issue of Geriatric Focus.

(4) Future Direction:

An extension of the above study, is being designed in which timing of illnesses will be studied in patients who die after age 75 and controls who died 10-20 years younger. It is anticipated that in the older more biologically elite that the majority of illnesses will cluster aroung the closing years of life whereas in the younger controls they will be spread over the entire life span.

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Effect of Thyroid Hormone on the Production and Peripheral Transformation of Steroids in the Aged Individual

The decrease in urinary neutral 17-ketosteroid excretion with age is universally recognized. The nature and qualitative characterization of such change is not so well understood. One group of workers (Gallagher, et al., Ann. N.Y. Acad. Sci., 86: 311, 1960) has demonstrated a changing androsterone/etiocholanolone (A/E) ratio in relation to thyroid function. Some of the earlier work in this laboratory showed a similar change in the chromatographic elution patterns of the 17-ketosteroids of older men (McGavack, et al., J. Amer. Geriatrics Soc., 3: 754, 1955). One or two pilot studies indicated that this might be corrected by the administration of androgen (McGavack, et al., J. Amer. Geriatrics Soc., 2: 489, 1954).

Questions raised which the present work is designed to answer include: (1) Is the decrease in urinary neutral 17-ketosteroids a straightline function of age? (2) What is the cause of the altered chromatographic elution pattern found in aging, particularly with reference to A/E ratio? (3) Is this change a primary one, related to gonadal or adrenal activity or both, or is it mediated specifically by way of the thyroid?

To answer the first of these questions three distinct studies have been carried out, involving a total of 309 human male subjects and 143 human female subjects, for a total of 452 individuals ranging in age from 3 - 87 years old (McGavack, T.H., Geriatrics 18: 181, 1963) (McGavack, T.H. and Hoch. H., J. Gerontol., 20: 383, 1965). A look at the data from full maturity (age 22) onward indicates an S-shaped curve of neutral 17- ketosteroids with a plateau from 22 to 40 years of age in both the male and the females and a steady decline from that point to the age of 60, after which levels for both sexes remain relatively constant - a type of curve later confirmed by others. The lowering of the A/E ratio with aging has been demonstrated in several studies of our own (McGavack, T.H., Geriatrics, 18: 181, 1963) and in those of others (Gallagher, et al., Ann. N.Y. Acad. Sci., 86: 311, 1960). While the cause for this lowering of the A/E ratio is believed to be a changing enzymatic pattern of hydroxylase activity on C_5 of ring I of the ketosteroid nucleus, this has not been proved. Part of our projected design will involve studies of these enzymatic changes.

A corrollary question has been concerned with the role of gonadal and of adrenal activity in causing the A/E changes observed during

aging. This question was originally raised when it was found that variations in thyroid function change such ratios (Bauer, H.G. and McGavack, T.H., J. Amer. Geriatrics Soc., 6: 880, 1958) (Gallagher, et al., Ann. N.Y. Acad. Sci., 86: 311, 1960) (Hellman, et al, J. Clin. Endocrinol., & Metabolism, 19: 936, 1959). A study is now in progress to determine whether or not processes of aging are also accompanied by changes in such ratios and also to explore the influence of thyroid status in the young as compared with the old in relationship to the ages studied. To accomplish this purpose a model has been developed which, in its simplest terms, involves the determination of 17-ketosteroids and A/E ratios in a representative group of young, vigorous adults between the ages of 20 and 40 in comparison with the same data obtained on a group of older individuals more than 60 years of age. Simultaneously, determinations are made of corticosteroid excretion, plasma levels for cholesterol, protein bound iodine and T_4 and the distribution of radioactivity in the urine following tracer amounts of ^{14}C-testosterone.

The model involves the determination of total 17-ketosteroids by previously described methods (McGavack and Hoch, J. Gerontol., 20: 383, 1965). A/E ratios are determined in two ways: (1) by column elution and thin layer chromatography, colorimetry and liquid scintillation spectrophotometry; and (2) by the measurement of radioactivity and its distribution following exogenously administered doses of ^{14}C-testosterone. In this part of the present study data to date are indicative of the fact that aging per se does materially lower the A/E ratio. As a part of the original plan, our models included the influence of the administration of T_3 to determine whether or not in old people thyroid hormone influences A/E ratios in a manner similar to that seen and already described for younger individuals. Since Gallagher and his associates have already made observations on younger people following the short term administration of large doses (200 µcg T_3 daily for 10 to 13 days), it was decided in the present model to include similar observations in older subjects and also to determine the influence of gradually increasing doses, eventually reaching a high level of administration. Data to date have shown that T_3 does influence the A/E pattern in the older subject in a manner similar to that seen in the younger individual. When gradually increasing doses of T_3 are used the effect is not striking until more than 125 µcg to T_3 are employed daily. Our observations on these points are still preliminary, but we believe correct. However, to be sure that a generalization can be made more subjects are already under study. It is interesting to note that, while not made an integral part of the models for these studies, thyroid hormone administered to aged subjects increases not only the A/E ratio but also the total amount of neutral 17-ketosteroids excreted in the urine. The reason for this increase is not at all clear. It could be a non-specific effect of thyroid hormone. However, further studies are contemplated to determine whether the action is thus non-specific or is mediated through a primary endocrine alteration. This will require an entirely

separate group of experiments with different design than that at present in use.

In our future work it is planned to complete the influence of thyroid hormones on aging patterns of 17-ketosteroids somewhat as outlined above. When this is done our immediate plans involve making similar studies of the THE/THF ratio changes, which are known to occur in adrenal gland secretion in relation to thyroid activity, but which have not been investigated as a function of age.

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Formation of Ketosteroids by Adrenals of Young and Old Guinea Pigs

Along with other changes associated with aging there are alterations in steroid metabolism and in various metabolic processes controlled by steroid hormones. Some of these are related to changes in adrenal function.

Quantitatively dehydroepiandrosterone is the major 17-ketosteroid secreted by the adrenal gland and it is probably the only quantitatively significant precursor of the urinary 17-ketosteroids. It has been shown that with aging there is a significant decline in urinary excretion of and plasma levels for 17-ketosteroids. In the present project, we have studied the enzymatic capability and factors involved in the formation of dehydroepiandrosterone from its immediate precursor 17a-hydroxypregnenolone by homogenates from adrenals of young and old guinea pigs.

The method of study involves homogenizing adrenals excised from male albino guinea pigs in Krebs-Ringer phosphate buffer and centrifuging the homogenate at 700 x G for 10 minutes. The supernatant and fractions from differential centrifugation of this supernatant to which cofactors are added are used for incubations with 17a-hydroxypregnenolone-7-^{3}H. The tritiated dehydroepiandrosterone formed is extracted and purified by a series of column and thin layer chromatograms. After purification the steroid is assayed colorimetrically by the Zimmermann reaction and radioactively by a liquid scintillation spectrometer.

Lipsett and Hokfelt using radioactive precursor 17-a hydroxypregnenolone incubated with human or with guinea pig adrenal slices were able to isolate labelled dehydroepiandrosterone in very low yield. The present study has given the first report of the influence of age on the formation of 17-ketosteroids (dehydroepiandrosterone) by adrenal cortical tissue. Results have demonstrated that the final step in the biosynthesis of dehydroepiandrosterone which involves the side-chain

cleavage of 17a-hydroxypregnenolone is age conditioned. A decreased production of dehydroepiandrosterone at this step could well account for the decline in 17-ketosteroid production and excretion with aging.

The conversion of 17a-hydroxypregnenolone-7a-^{3}H has been demonstrated and its significance studied. The conversion required a hydrogen-generating system and occurred quite rapidly at pH 6.88.

Through continuing work it has been shown that, after differential centrifugation of adrenal homogenates, the unwashed mitochondrial fraction is the one most actively involved in the formation of dehydroepiandrosterone from 17a-hydroxypregnenolone. Omission of any individual salt from the Krebs-Ringer phosphate buffer did not appreciably affect the synthesis.

Further work is anticipated with washed mitochondria in order to establish cofactor needs and the effect of inhibitors.

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Aging in Connective Tissue II. Ground Substance a. Urinary Carbohydrate-Protein Complexes (CPC)

A systematic study of the urinary carbohydrate-protein complexes of normal subjects has been published from our laboratory in the past two years. The method is simple and the treatment is mild. All components preserve their natural form and are suitable for further fractionation.

Urinary carbohydrate-protein complexes (CPC) are fractionated into CPC-I (Tamm and Horsfall mucoids), CPC-II (glycoproteins) and CPC-III (glycopeptides and acid mucopolysaccharides). The latter two fractions may be further fractionated into their ultimate components.

Our results were in agreement with those published by Bourrillon and Dische in that we found urinary glycoproteins to consist of a large number of glycoproteins with widely varying molecular size and composition. By employing disc electrophoresis, we further demonstrated an even greater multiplicity of components than had previously been suspected. We also have been the first to report age differences in the amounts of urinary glycoprotein. In the study of urinary AMP we have been the first group to demonstrate the pattern of naturally bound AMP and its resistance to enzymic digestion in samples from aged subjects.

Our method is now being used to study urine from various types of diabetics and of controlled, uncontrolled and ketotic subjects. As time may permit, it is planned to use this method to study urine from patients with connective tissue diseases.

The most common complications associated with diabetes mellitus are concerned with arterial disease. Basement membranes become thickened. Histologically, Schiff's staining substances increase. Such change is especially prominent in the kidney and retina. It would be interesting to see if there is any effect on CPC excretion in the urine. Preliminary results have indicated that there is no change in total amount of CPC-I, II and III in the urine. Qualitative differences in the components are under investigation.

In addition to the published method, a micro method for the separation of acid mucopolysaccharides is being tried experimentally. Preliminary data revealed that a mixture of 100-500 μg acid mucopolysaccharides may be quantitatively separated. This method may be used conveniently for the study of changes in AMP metabolism in tissue or urine in various diseases.

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Aging in Connective Tissue II. Ground Substances
b. Changes in the Composition of Ground Substance During Aging

Conclusions have been drawn about differences in ground substance with age as a result of the determination of hexosamine or uronic acid. Since ground substance is composed of a mixture of carbohydrate and protein complexes, such conclusions may easily be erroneous. Furthermore, the nature and amounts of acid mucopolysaccharides vary from tissue to tissue. Variations in the amount of uronic acid are indicative of a change in AMP. Hexosamine is a constituent of both AMP and glycoprotein. Therefore, a change in hexosamine is uninformative as it may indicate an alteration in AMP or in glycoprotein. In order to understand clearly age differences in ground substance, we are trying to separate ground substance proteins into their individual components and then to evaluate changes in such components in relation to age. The rib cartilages of rats have been used for this study. AMP rich protein is separated from other proteins by 1) solubility differences, 2) determination of composition by physicochemical means, and 3) age differences in these proteins.

Rib cartilages of rats were cut into small pieces. Ground substance protein was extracted with water as described by Schubert. Ammonium sulfate was added to 55% saturation. The AMP-poor proteins, i.e. glycoproteins (GP), were precipitated and the AMP- rich protein, i.e. chondromucoprotein (CMP), remained in solution. The ultracentrifuge, Sephadex columns, disc electrophoresis and paper electrophoresis were used to study its composition. Protein, hexose, uronic acid, hexosamine, sialic acid and fucose were determined.

Preliminary work done on rats at several ages showed that there was a decrease of 50% in CMP from 3-4 months to 10-11 months of age. The change in GP with age is much less than that in CMP.

The ultracentrifugal pattern of the CMP was relatively pure with a single peak, while the GP fractions proved to be multicomponent. Sephadex G-200 column chromatography and disc electrophoresis were tried for the separation of the GP. The GP was excluded from the Sephadex G-200 column and was not able to pass through the gel. Since ultracentrifugal data revealed the multicomponent picture, a gradient centrifugation was suggested as the method of choice for such separation. Chondromucoprotein is a well known component of cartilage. The importance of GP, which is neglected by most investigators, will be stressed in our work on ground substance.

The chemical composition of both CMP and GP are under investigation. Both fractions are rich in hexose. This agrees well with our urinary AMP study. All AMP are rich in hexose. The hexose and hexosamines will be identified. This method will also be used to study ground substance in other tissues.

Previous data on rat rib cartilage from this laboratory revealed that there was a glycoprotein tightly bound with collagen which increased with increasing age. The composition of this protein and age differences in the composition of these carbohydrate complexes will be investigated. In order to understand the changes in ground substance in various diseases, the present study is designed 1) to determine the normal composition and structure of these carbohydrate and protein complexes, and 2) to find quantitative and qualitative changes in these complexes during aging.

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Gastrointestinal Absorption of Calcium in the Male Using Calcium 47 and Calcium 45

Introduction: Many of the factors affecting calcium absorption by the human gut in health and disease states are incompletely understood and present a serious problem in the geriatric patient. Metabolic balance procedures attempting to study this aspect of calcium metabolism are difficult, frequently inaccurate and usually require a minimum of 2 to 3 weeks of careful metabolic balance studies. In addition, net calcium absorption or the difference between the mean daily ingested calcium and the amount occurring in the stool does not assess that part of the calcium derived from its secretion into the gastrointestinal tract, which may be a considerable fraction in some cases.

A number of disease states are associated with abnormal gastrointestinal absorption of calcium, the most common being malabsorption due to primary gastrointestinal disorders of various etiologies: sarcoidosis; uremia; idiopathic hypercalcuria; parathyroid disorders; and resistant rickets or osteomalacia.

The evaluation of malabsorption, in general, is difficult because of the limited number of tests available and the limitations of the tests themselves.

At this hospital the following tests may be used to measure various aspects of malabsorption: RAI triolein, RAI oleic acid, serum carotene, Schilling test (in special cases) and the stool fat (72 - hour collection). None of these tests, except possibly the measurement of stool fat on a constant fat intake, can be considered as conclusive evidence of malabsorption. The addition of another test, if practical and reliable, may be of value in the diagnostic armamentarium available in this hospital.

Recently calcium 47, an isotope with a half life of 4.7 days, which is easily measured because of its emission of gamma rays, has become available and has been used by several investigators to study calcium absorption by the gut.

In 1961 Bhandarkan et al utilized calcium 47 to measure intestinal calcium absorption by plasma radioactivity levels at ½ hour intervals after ingestion of the dose. Miller et al also reported the results of a similar test method in 1962. Subsequently, Jaworski et al in 1963 reported a study in which, in addition to plasma radioactivity levels after ingestion, the percent radioactivity absorbed by the gut was used as a second parameter. This latter value was calculated by collecting all of the stool and urine for 6 days after the ingestion of the dose, the absorbed radioactive calcium then being equal to the total dose administered minus the total radioactivity excreted in the stools and urine over a 6-day collection period. These investigators demonstrated that by correlating both parameters the range of normals and abnormals could be separated. Avioli et al in 1964 and in 1965 described a 4-hour procedure and reported its use in 25 normals and in 26 patients with known abnormalities of calcium absorption. Their results demonstrated that 4-hour plasma and urine radioactivity values following a standardized dose correlated significantly with percent absorption calculated from 6 day stool collections following the dose of radioisotope. They suggested using the plasma and urine values alone as a reliable measure of absorption of calcium. A double isotope method using calcium 45 orally and calcium 47 intravenously was used by De Grazia and Rich in 1964 to separate the contribution in the stool of the

endogenously secreted portion of the fecal calcium following an oral dose of calcium 45. This contribution was found to range from 1 to 7% with a mean of 3.3% in the patients without calcium or phosphorus derangements. This portion of the fecal calcium after a standardized dose of radioactive calcium may thus be of importance in some cases.

The purpose of the present study is to utilize calcium 47, primarily because of its shorter half life (4.7 days) and ease of measuring its gamma ray emission, orally to study the absorption of calcium by the gastrointestinal tract in male subjects without diseases affecting calcium and phosphorus metabolism. A range of normals, using the parameter described below, could then be established for this laboratory. In addition, a significant number of normal subjects will be given calcium 45 intravenously at the peak rise of radioactivity following the oral dose of calcium 47. The stools will then be measured over 6 days and the urine collected over the same time so that endogenous secretion of calcium into the intestinal tract can be calculated. If reliable normal ranges can be established, subsequent correlation of absorption of calcium with age in the male can be studied. Future studies then will include patients with disease states associated with abnormal calcium or phosphorus metabolism. Emphasis will be placed on osteoporosis in the male and the relationship of calcium absorption by the gastrointestinal tract in these patients as compared to non-osteoporotic subjects of similar age groups. These relationships in the male have not been studied to date, although they have been partially studied in the female.

Methods of Procedure: Initially, hospitalized male patients without disease states affecting calcium and phosphorus metabolism will be studied. An attempt will be made to vary the age distribution over as wide a range as possible. All subjects will be transferred to a metabolic room and placed on constant caloric and calcium intakes. The latter will range from 300 to 1500 mg. per 24 hours and will be maintained constant for each subject. To ascertain the accuracy of dietary estimation duplicate diets will be prepared, homogenized, and measured for calcium and phosphorous. After a minimum of 6 days on their respective diets, the patients will be studied after a 12 to 15 hour overnight fast. Baseline serum calcium, phosphorus, alkaline phosphatase, creatinine, BUN, hematocrit, total protein, albumin and globulin values will be obtained. A heparinized blood sample will also be drawn for background radioactivity. Patients will then be given 30 microcuries of calcium 47 mixed with 20 mg. of calcium ion as the chloride in 100 ml. of distilled water as near to 9:00 a.m. as possible. Blood will then be drawn in a heparinized syringe at 30, 60, 90, 120, 180 and 240 minutes and measured for radioactivity. Results will be reported as percent of

administered dose per liter of plasma per square meter body surface. Just prior to receiving the dose of calcium 47 the patients will completely empty their bladders. Urines will then be collected at 2, 4, 8 and 24 hour intervals. Daily urines will be collected for 7 days after the initial dose. Stools will be collected over a 7-day period and measured for radioactivity. When possible, they will be collected in daily separate portions.

Analysis of Data: The following parameters will be used to estimate calcium absorption by the gut: (1) Radioactivity in the plasma following the oral dose measured as percent of administered dose per liter of plasma per square meter of surface area. Peak values in normal subjects will be observed; (2) Urine excretion of calcium 47 measured in the first 2, 4 and 16 hour samples. The sum of all the values making up the first 24 hour urine excretion, as well as the total for the entire 7-day period, will also be calculated; (3) Cumulative 7-day fecal radioactivity and, where possible, daily fecal radioactivity will be measured; (4) The sum of the urine and fecal 7-day excretion of calcium 47 will be subtracted from the total administered dose and this value will then be used to calculate the retention of radioactive calcium in each subject.

These parameters will be correlated to obtain those which appear to be most accurate to measure the absorption of calcium by the gastrointestinal tract. The use of calcium 45 intravenously will be reserved for those cases in which correlation of these parameters is not significant and in selected cases to calculate the endogenous secretion of calcium into the gastrointestinal tract.

Facilities Available: The Radioisotope Laboratory at the Veterans Administration Hospital, Livermore, is well equipped to count the specimens obtained by the above methods. Dr. Robert Hansen, Chief of the Radioisotope Laboratory, and Dr. Harold Murdock, Research Pharmacologist, are assisting in this investigation.

Normal subjects may be obtained on the hospital ward. Consent slips with complete explanation of the studies involved and the diets used will be made for each patient. With regard to the radiation hazard of the administered radioisotopes, calculations made by Jaworski showed that the total dose delivered to the active bone marrow by calcium 47 when 30 microcuries are given (this will be our maximum dose) average 500 millirad per test. This would be equivalent to less than the average radiation dose to the bone marrow which occurs when I-131 thyroid uptake studies of x-ray pyelography are performed.

Supporting Data: Dr. Magid has performed 17 studies on the absorption of calcium using the 4 hour plasma and urine radioactivity

method, described by Avioli et al, in 16 outpatients to date. These included 13 normal subjects, one patient with a parathyroid adenoma who was studied before and after surgery and the two patients with Familial Hypophosphatemia. An oral dose of calcium 47 was given exactly as described in this protocol to each subject and measurements made at 30, 60, 90, 120 180 and 240 minutes. Urines were collected in two 2 hour periods following the dose. All studies were performed in the post absorptive state.

Conclusions drawn from the above results are preliminary at present, however they suggest the following:

1. Our ranges for plasma measurements are higher at the maximum levels than those observed by Avioli. However, our ranges appear to be relatively narrow and workable.

2. Calcium absorption in the patient with the parathyroid adenoma shows a slight tendency to higher plasma radioactivity, suggesting increased absorption of calcium although this does not appear statistically significant.

3. Avioli's two cases of hyperparathyroidism do not show significantly increased plasma radioactivity except in one case at 30 minutes.

4. Urine measurements in our normals have lower minimum values than do Avioli's.

5. The parathyroid adenoma in our series shows significantly elevated urine values pre-op, unlike Avioli's two cases, and these values return to low normal values post-op.

6. The values, both for plasma and urine radioactivity following the oral dose, in the 2 patients with familial hypophosphatemia fall within the normal range.

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Studies of Normal and Abnormal Motion

The several areas under investigation entail studies of various properties of motor performance of normal subjects and disabled patients. The properties of motor performance include: walking ability; muscle strength; postural steadiness; balancing ability; and muscle rigidity. Initially, the design of each of these studies

of motor performance invariably requires our obtaining standards of normal values for the motor performance since these are rarely available. Once the normal standards are available for comparison, we are able to identify the degree of deficit in performance of patients with specific disabilities; and we are able to measure the effectiveness of various medical and surgical treatment procedures on the disordered motor performance.

Studies of Walking Patterns: For our original studies of walking patterns, we developed a strobo-photographic method of recording the simultaneous movement patterns of the limbs, head, neck, and trunk in two planes of space. We applied this method to obtain normative data for 16 simultaneous displacement patterns for free speed walking of men in age groups from 20 to 65 years. The subjects in each age group were of similar weight and stature. We expected that the free speed walking patterns of the subjects in the different age groups would be strikingly similar. However, analysis of these data revealed that several of the gait components of the normal men in the oldest age group from 60 to 65 years were notably different from those of the younger men. The free speed gait patterns of the sixty year old men were characterized by shorter and wider stride dimensions than the younger men and by decreased motion of the ankle, hip, pelvis, and head. These differences suggested a "pre-senile" walking pattern.

In a subsequent study of upper limb movement during walking of normal men from 20 to 65 years, we noted that the 60 year old subjects also showed diminished amplitudes in their arm swing movements. In another separate study of normal walking patterns we found that several aspects of the vertical pathways of the heel and toe of the 60 year old men were different from younger men. In a fourth study comparing twenty simultaneous gait patterns for free and fast speed walking of normal men, we found that the previously suggested "pre-senile" patterns were even more pronounced for fast speed walking.

We are also studying the gait patterns of normal women in order to obtain baselines for comparison of the disabled females who are being referred to us for gait evaluation. Preliminary observations of these data suggest that the gait patterns of the 60 year old women also differ from those of younger women.

Accordingly in a current study we are expanding the upper limits of our age range to include normal men of similar height up to age 87 years in order to determine if the previously suggested "pre-senile" patterns of the sixty year age group are consistent and progressive with advanced age.

If the gait patterns of normal aged subjects prove to be characteristically different from younger subjects, direct application of this information seems apparent. These data will provide revised standards of reference which will be more appropriate for comparison of disabled patients of advanced age. These data may suggest more realistic therapeutic goals for the increasing numbers of aged patients with physical disabilities which impair walking performance. Moreover this information may be useful in the design of more optimal assistive devices for walking (artifical limbs, braces, crutches, canes, etc.) in order to more adequately fulfill the needs of disabled geriatric subjects.

Muscle Strength Studies: We are currently completing a study of the isometric strength of the hip abductor and adductor muscles of normal men and women. We have completed measurements of maximum joint torque produced in various positions in the hip joint on a large sample of subjects in age ranges from 18 to 55 years. This study has been designed to provide normal standards of reference for comparing the strength deficits of patients with hip joint disorders before and after selected surgical procedures. For almost all of our test conditions, we are finding that the strength of the men and women older than forty is significantly less than that of the younger subjects. Since many of our patients with hip disabilities are between their 5th and 8th decades of life, again it appears that we must extend the upper limits of our age range to provide adequate baselines for comparison of disabled patients.

Postural Steadiness, Balancing Ability, and Muscle Rigidity: We are now initiating extensive normal standard studies of postural steadiness, balancing ability, and muscle rigidity. Each of these studies will be designed to assess the influence of advanced age on the properties of motor performance.

Hans Naumann
Veterans Administration Hospital
Memphis, Tennessee

Chemical Changes of Aging

Investigations on postmortem chemistry have been in progress for many years (Arch. Path., 47:70, 1949; Amer. J. Clinical Path., 20:314, 1950; Amer. J. Clin. Path., 26:495, 1956; Proc. Soc. Exp. Biol. Med., 98:16, 1958; Arch. Ophthal., 62:356, 1959; Proc. Soc Exp. Biol. Med., 105:70, 1960; Cerebrospinal Fluid, Postmortem vs. Antemortem: Man, in Altman, P.L., and Dittmer, D.S.: Blood and Other Body Fluids, Washington, 1961, p. 319) originally with the

object of determining the cause of death in cases where autopsy findings are few or inconclusive. For instance, in death from diabetic coma the changes of internal organs may be insignificant, yet the high concentration of sugar and acetone in cerebrospinal fluid indicates diabetes as cause of death. In the course of these investigations some observations have been made also on chemical changes of body fluids and tissues due to aging. However, little is known of the chemistry even of apparent old age pathology such as clouding of the lens of the eye, calcium loss from bones, fat deposits in blood vessels or loss of elastic fibers from the skin. Purpose of the present research is the systematic study of the chemistry of such changes in order to elucidate the mechanism of the aging process.

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Chicago, Illinois

Amino Acid Analogs and the Etiology of Collagen Disease

Aging involves alterations in the molecular structure of many tissues. Collagen, which is a part of connective tissue, undergoes some changes in the process of healing, growth and aging. The alterations in collagen structure are being evaluated by in vitro methods in rats and in tissue culture. The chemical linkage of the amino acids is studied by physical chemical methods involving column chromatography, ultracentrifugation and separation in amino acid analyses. The various amino acid analogs are labelled with C^{14} or H^3. The appearance of the labelled analog in various positions along the structural chain can thus be shown.

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Jefferson Barracks, Missouri

The Relation Between Social Behavior Pattern and the Functional Aging of Humans

It is a common observation that characteristic aging changes occur to different people at different rates. Some biologists (e.g., Tamplin and Verzar) have suggested that both insight into and some control of the aging "process" may result from a type of study that makes comparisons between individuals of a given age who seem to have senesced more rapidly and less rapidly. Some social scientists (such as Birren and Kuhlen) have suggested that behavior and adjustment may be major independent variables which influence the course of the aging process. The line of research initiated by this study

is directed toward identifying a set of behavioral factors which seem to hasten aging or delay it. The specific question addressed here is: Do individuals who seem young for their years differ from those who seem old for their years, with respect to social behavior patterns exhibited earlier in their lives? Behavior is conceptualized as "transaction between an individual and his impinging environment" (both social and physical).

In applying the transactional approach to social research problems, it is assumed that despite the decrements that are usually seen to accompany aging, there is still some adaptive, compensatory, or "growth and development" potential left in the aging human organism, generally more so in the non-physical realms. For the purpose of this study it is postulated that human development is enhanced or diminished by the amount of transaction an individual has with his environment, especially the human part of it. It is also taken as a reasonable assumption that the same factors which enhance development retard aging. These factors are seen as including the qualitative variations in social behavior patterns ("coping problems"); in the qualities, demands and growth potential in the environment; in the match between coping abilities and environmental demands; and in the amount of transactional exchange between the individual and his environment.

Although the theoretical model treats transactional behavior as an independent variable and functional aging as the dependent variable, this is essentially an exploratory study of the correlational type, and later confirmation of the directional influence required.

A non-probability sample of 74 male ambulatory hospital subjects was selected to represent four age cohorts -- 40, 50, 60 and 70 years old. A special schedule was developed for assessment of functional age on the basis of fifteen physiological and anatomical criteria, which were derived from relevant literature and biological consultation.

Examination and testing were completed with the help of medical and nursing personnel. Preliminary analysis indicated that eight of the criteria were sufficiently age-related in the sample to serve as a basis for computing each subject's functional aging index score, in order to contrast it with his chronological age.

An activity inventory was developed and administered to obtain data for assessing the quantitative aspects of the subject's past social transactions. A classification of social activities is to be formulated in accordance with the special social work frame of reference that is being developed in this research.

For the purposes of a substudy, photographs were made of a number of subjects in order to investigate the relation between their age appearance and their scores on the index of functional aging.

The data on the 74 subjects are currently being analyzed with the assistance of computer facilities provided by the southern research support center. Multiple regression analysis and T-scaling are being used as alternative methods to arrive at an aging index, as a basis for computing discrepancies between actual chronological age of subjects and their functional age, in order to identify subjects who can be considered old and young for their years. It will then be possible to determine if those subjects who measure young for their years differ in amount of reported activity from subjects who measure old for their years. Qualitative differences in activity will be analyzed when the activity classification is constructed.

Lajos Piko
Sepulveda Veterans Administration Hospital
Sepulveda, California

Properties and Function of Mitochondrial DNA in Relation to Development and Aging

Mitochondria occur in nearly all cells of plants and animals; their basic role in energy metabolism is well established. Current research indicates that mitochondria also have considerable biosynthetic activity. The recent demonstrations that mitochondria carry their own genetic material (DNA) establish them as a separate cytoplasmic genetic system that functions semi-independently of the nuclear genome. Since the cytoplasmic location of mitochondrial DNA makes it more sensitive to environmental agents that may cause mutations, this DNA appears to be one of the primary candidates for the site of changes responsible for cellular aging.

Our own research (Piko *et al.*, 1967) on mitochondrial DNA of sea urchin eggs was among the first to show that this DNA consists of double-stranded, covalently closed circular molecules of a uniform size of about 5 microns. Similar results were obtained earlier for mitochondrial DNA of mammals and birds (Borst *et al.*, 1966) and, later, amphibia (Dawid and Wolstenholme, 1967). Currently research is in progress in a number of laboratories on mitochondrial DNA's from various other sources. The properties of the mitochondrial DNA circles are very similar to those of the circular DNA's of some viruses (several of which are known to induce tumors). Recently if has been shown that a certain proportion of

mitochondrial DNA circles are linked together into chains consisting of two or more circles. Such DNA chains have been observed (Hudson and Vinograd, 1967) in HeLa cells (cultured human cervical tumor cells), leucocytes of leukemic patients (Clayton and Vinograd, 1967) and sea urchin eggs (Piko et al., 1968). The significance of these unique molecules is not known as yet. The fact that they occur in sea urchin eggs indicates that they are not per se associated with abnormal cells, such as tumor cells. In order to shed light on the correlation between structure and function of mitochondrial DNA, we are at present studying the changes that occur in the amount and kind of mitochondrial DNA molecules during development and differentiation of sea urchins and some other lower animals. The sea urchin is particularly favorable material since large numbers of embryos that are synchronized as to stage of development can be obtained. The basic observations and research methodology that are derived from this research will be applied to the study of development and aging in laboratory mammals. Parallel tests will also be made with human and other primate material, as the exploration develops and as such material becomes available and amenable to the kinds of analysis that would provide further insight into relationships to pathogenic processes and aging. The present investigations include parallel studies on the fine structure of the mitochondria by electronmicroscopy to provide insight into questions of morphogenesis and differentiation of mitochondria with respect to properties and amount of DNA that they contain. Tests of possible effects on development in mammals are now made more feasible in our laboratory by the organization of a unit that is concerned with the culturing and re-implantation of mouse eggs. In this system the investigations are directed towards the possibility of influencing the development and life cycle of the individual in specific ways by means of the various DNA's and RNA's.

Hubert Pipberger and Edward Fries
Veterans Administration
Washington, District of Columbia

Demonstration of Aging Processes of the Cardiovascular System by Non-Traumatic Recording Methods

Development of relatively simple recording methods to indicate age-related changes of the cardiovascular system have become of increasing interest in recent years, particularly in population studies. It appears desirable to make methods available which would reveal aging processes of the heart and the vascular system. Deviations from mean changes, encountered in given age groups, may prove of significance for the prediction of cardiovascular accidents. Since such predictors have to be validated in large population studies, non-traumatic procedures are preferable for obvious reasons.

To demonstrate age-related changes of the heart the electrocardiogram was chosen because of its general availability and ease of application. A relatively simple method for documenting age changes of the vascular system consists of pulse wave contour analysis. Such records can be obtained from externally applied transducers. The ECG part of this study is performed under the direction of Dr. Hubert V. Pipberger, the pulse wave study under Dr. Edward D. Freis. Both, ECG and pulse wave tracings are taken on magnetic analog tape, converted into digital form and analyzed by digital computer.

Age Changes of the Electrocardiogram
(Hubert V. Pipberger, M.D.)

Age-related changes of the heart are mainly due to two anatomic-pathologic developments. Increase in coronary atherosclerosis with advancing age is probably the most important factor, leading to replacement of myocardial fibers by fibrous tissue. Although it is only reasonable to consider this disease process as a major factor in the aging process of the heart, it is probably an oversimplification to regard it as the only cause. Other aging factors that are less well defined, may also contribute, leading to gradual myocardial degeneration or senile atrophy with loss of large numbers of fibers and reduction in weight of the senile heart. The latter process can be seen in cases with little or only moderate coronary atherosclerosis.

Both of these processes, progressive myocardial fibrosis and myocardial degeneration with senile atrophy lead to diminution

in number of active myocardial cells. As expected, this causes a decrease of the voltage of the body surface ECG with age. This phenomenon was studied in 518 subjects without past or present evidence of cardiovascular disease, ranging in age from 21 to 78 years. When the sample was divided in decades an average decrease in voltage of 6.5 percent was observed for the QRS complex and a 9.75 percent decrease for the ST-T complex. This average diminution in ECG magnitude appeared linear, i.e., the aging process did not show any acceleration in late decades nor a slower progression in young adults.

In order to determine optimal ECG indicators of the aging process, correlation coefficients between age and 333 different ECG measurements were computed. Seventeen parameters correlated at a level between 0.3 and 0.4. Using multiple regression analysis with 3 ECG variables, a correlation coefficient of 0.45 was obtained with a standard error for age of 11.12 years. Although this result is highly significant statistically, the scatter of individual findings is still too large for prediction of age in a reasonably narrow range. The electrocardiogram which is basically only a very indirect indicator of cardiac function, cannot be expected to yield any closer correlation. The relative position of an individual, in a scattergram of age and ECG measurements or his deviation from the mean age may serve, however, as predictor in terms of morbidity and mortality.

In order to test this hypothesis ECG records from the Albany Cardiovascular Health Center are being used. This study, under the direction of Dr. Joseph Doyle, is based on 2500 employees of the State of New York, between the ages of 40 and 60. Their annual electrocardiograms, recorded on magnetic tape, are mailed since 1964 to VAH Washington, D.C., for computer analysis. The deviations of each individual case from that expected for his chronologic age, are being evaluated in terms of morbidity and mortality. Although preliminary results of this longitudinal study appear promising, a follow-up over a longer period of time is needed in order to draw final conclusions.

A corollary to this study consists of analysis of high-frequency components of the electrocardiogram. This investigation is based on the observation that such components are significantly increased with advancing age. The question which remains unanswered is, whether these changes are solely due to coronary artery disease or whether they can also develop in its absence. Detailed pathologic examinations of the heart are necessary for this study. Such detailed material will become available to us after July 1, 1968, from the Department of Medicine, UCSD, under the direction of Dr. Eugene Braunwald, where a full-time pathologist will be in charge of the correlations with the electrocardiogram.

Age Changes of Arterial Pulse Wave Contours
(Edward D. Freis, M.D.)

It has been known for some time that aging is associated with a reduction in the distensibility of the aorta and large arteries. More recently it could be shown that these age-related changes may be detected in man from externally applied transducers. In addition to providing a possible index of arterial aging, external pulse wave recordings are of interest for the following reasons: 1. They can be recorded by a trained technician; 2. Improvement in transducers has facilitated the obtaining of good quality records; 3. Magnetic tape recording followed by computer analysis permit processing of large volumes of recordings, an important consideration in population surveys.

A novel type of transducer was designed for the present study in cooperation with the National Bureau of Standards. Original studies of age changes of pulse wave recordings were made primarily on the carotid artery. More recently the brachial artery was included. It is less subject to artifacts produced by respiratory and other movements or by venous pulsations as is the carotid.

Recordings were taken from 228 male subjects without past or present evidence of cardiovascular disease. The age ranged from 15 to 90 years.

The principal age-related changes in the carotid pulse waves were an increase in the amplitude of both the incisura and the second systolic maximum rleative to the first systolic maximum. Although the mechanism of these changes has not been completely elucidated they probably reflect at least in part the decrease in distensibility of the central arterial system which occurs with aging.

In addition, the brachial pulse also exhibited characteristic changes with age. The most significant was a decrease in amplitude and duration of the dicrotic wave. The brachial pulse wave was somewhat easier to record than the carotid which makes this recording site ideally suited for large-scale population studies.

When various pulse wave measurements were correlated with age, correlation coefficients up to 0.60 were obtained for the carotid and up to 0.65 for the brachial artery. In view of the higher correlations between age and pulse waves than those found for the electrocardiogram this recording method promises to become an

even more efficient means for prediction of vascular accidents which increase regularly with advancing age. Does the individual with a pulse wave configuration "older" than his chronologic age already have the beginning of vascular disease? Longitudinal studies similar to those in progress for electrocardiograms, will be needed to answer this important question.

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Auditory Concept Identification as a Function of Age and Sex

Recent research in concept identification (CI) utilizing auditory dimensions with adult subjects indicates that there are sex differences in CI performance and that females reach solution at a significantly higher rate than males when laterality is the relevant dimension (Pishkin & Blanchard, 1964; Pishkin & Shurley, 1965). In the same experiments it was shown that the intensity dimension was more difficult to categorize than dimensions of number, laterality, frequency or duration. Since previous results are based on adult populations, it was speculated that sex differences may stem from developmental factors and are due to adult females' narcissism and their sensitivity to body stimuli (Pishkin & Shurley, 1965). Thus, it is hypothesized that as children grow older, males show poorer performance on laterality as compared with females.

The experiment focuses on saliency of five different auditory dimensions in an attempt to examine the function of subject's sex and age in auditory CI. The subjects are 200 males and females who perform on an auditory CI task to a criterion of 16 correct consecutive trials for a maximum of 192 trials. The stimuli are presented through earphones worn by subject who sits in front of a panel with two response buttons with feedback light directly above each button. The subjects are told to categorize each stimulus into one of two categories by depressing a response button and that the feedback lights indicate the correct response. The task is self-paced and the sequence of events are as follows: (1) presentation of auditory stimulus, (2) subject's response, (3) feedback light on for 1 sec., (4) 3 sec. silent interval and (5) presentation of next stimulus. Subject's responses, feedback, response latency and type of stimulus are recorded on the Esterline Angus 20 pen operations recorder. This is a 5 x 4 x 2 factorial design with 5 auditory dimensions (number, intensity, laterality, frequency, and duration); 4 age groups and sex with equal number of male and female subjects

randomly assigned to age and dimension conditions. Duncan's tests and Multiple Range Analysis are used on main effects.

The bileveled dimensions vary in the following manner: number (one or two tones with 2 sec. interval between them); intensity (65 or 80 db Sound Pressure Level, 250 cps); laterality (sound is presented on either left or right earphone; frequency (250 cps or 1800 cps); duration (1 sec. or 3 sec.). Only one dimension varies on any specific problem, e.g., when number is relevant, stimuli consists of one or two sounds and the first level listed for other dimensions is consistently presented, i.e., 65 db, 250 cps, 1 sec., with the exception that sound is presented through both earphones when laterality is irrelevant. The sequence of stimuli and feedback are programmed with a Western Union punch tape-transmitter controlling the sound generator (Pishkin & Shurley, 1965).

Clayton Rich
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Seattle, Washington

Versine Infusion Test in Osteoporosis

We have analyzed the rate of recovery of the blood calcium concentration after a dose of trisodium, hydrogen ethylene diaminetetraacetic acid, given under standardized conditions. The data fit a single exponential recovery rate, from which a miscible pool and a calcium transfer rate can be calculated on the basis of a single pool exponential model. We find this to depend upon bone cell metabolic activity rather than the exchangeable calcium of bone, as defined using ^{47}Ca.

The objective in this work will be to evaluate the results of this procedure in subjects with osteoporosis, comparing them with bone mass measured by an x-ray densitometive technique and the histological appearance of bone obtained on biopsy. This project is importantly related to gerontology because osteoporosis is an age-related disorder of bone and significant cause of morbidity in older persons. Our objective is to see if there is any abnormal pattern of bone cell response in osteoporosis which would contribute either to our understanding of or ability to diagnose the disease. Work is in an early stage and no correlation of the results will be attempted for about one more year.

Frank Schlenker, Julio Goldenberg and
Michael Gompertz
Veterans Administration Hospital
Memphis, Tennessee

Biochemistry of Intestinal Tissue

Components of the diet supply materials for the production of energy and formation of new or replacement tissue. Feeding habits of individuals change from birth through maturity to old age. The Biochemistry Section is engaged in a comprehensive study of the intestinal tract to ascertain the metabolic processes and cycles through which fats, proteins, and carbohydrates must pass after absorption before entering the mesenteric blood supply.

The technique being developed employs an instrument in which whole pieces of intestinal tissue can be exposed to a buffer containing a food element, e.g., glucose, and by varying the oxygen and nitrogen in the system, aerobic and anaerobic situations can be established.

Through the employment of this device it is possible to study various metabolic processes from birth through old age in the mucosa of animals.

Ernest Schwartz
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Clinical Physiology of Bone: Effect of Hormones and Vitamin D

The main objectives of our research have come to concentrate upon the physiology of bone resorption, a phenomenon which appears to be at the core of wasting bone diseases in the aging patient, in particular -- the osteoporotic syndromes. Our early studies with high calcium intake in osteoporotic patients demonstrated initially positive calcium balances. However, prolonged high calcium intake eventually resulted in attainment of calcium balance, without obvious clinical or radiologic change in the status of the patients. Serial radiocalcium kinetic studies suggested that the observed positive calcium balances were due to inhibition of bone-resorption, perhaps due to inhibition of parathormone action. The data further showed that calcium equilibrium occurred as the result of a delayed, coupled reduction of bone-formation rate, which would, therefore, explain the failure to gain bone mass during high calcium therapy.

Our studies have been extended to include the effects of estrogen upon bone physiology. Estrogen has long been considered to be an anti-bone-resorptive agent, useful in post-menopausal osteoporosis. We have demonstrated the effectiveness of estrogen in reducing the hypercalciuria of an oophorectomized female, and in reducing the radiokinetic indicators of excessive bone resorption in this patient. In our hands, estrogen has successfully reduced the hypercalcemia of multiple myeloma, of metastic hypernephroma, and of hyperparathyroidism, by reducing the excessive bone resorption associated with these diseases. Estrogen also seems to be of value as a Vitamin D antagonist in the abnormal calcium metabolism of sarcoidosis, but this conclusion is not as yet firm.

Our studies thus far indicate that estrogen is of general value as an anti-bone-resorptive agent, being effective in diverse states of excessive resorption. Its effects upon bone formation appear to be secondary to those upon resorption, and bone formation almost uniformly declines when excessive resorption is controlled with estrogen therapy. In certain osteoporotic states, the decline in bone formation appears to drop to subnormal levels, indicating the reason for failure of estrogen to rebuild bone in osteoporosis.

Sant S. Sekhon
Veterans Administration
Long Beach, California

The Process of Aging in the Central Nervous System of Mouse

There is remarkably little in the literature on the electron microscopy of the aging process in the central nervous system. What exists is in the form of casual observations and comments of general nature. Today we know little more than we did prior to the introduction of the electron microscope to study of the brain. It is generally believed that aging neurons accumulate pigment granules or lipofuscin. Electron microscopy has confirmed this, and permits a close examination of the granules. But the process by which they are formed and their significance is uncertain. It is a widely held view that lipofuscin is a product of the wear and tear mechanism in the cells. At the electron microscope level these granules show resemblance to lysosomal residual bodies seen in other types of cells. Whether they are such, whether they are enzymatically active, and the function of their lysosome precursors if they are such, should be investigated at the electron microscope level.

There is an enormous species variation in the amount of pigment present in neurons, as well as great regional differences, and an electron microscope examination of the aging process should be carefully designed to minimize the effects of these riddles. The role of neuroglia and other factors in the neuronal environment may be relevant to the ability of the neuron to survive aging, or to respond to it. This aspect should be explored ultrastructurally and observations may be capable of being related to the modest body of histochemical literature on the subject at the light microscope level.

Curtis (1963) has recently hypothesized that the effect of irradiation on tissues generally and the nervous system in particular is to accelerate the aging process. It would be of interest to test this model of aging morphologically by relating irradiated tissue to aged brain tissue.

It is proposed to employ standardized methods of tissue preparation which have proven satisfactory in other experimental series in which it has been necessary to minimize morphological variations due to fixation. To minimize the species variation problem a closely inbred strain of mice will be exclusively used. A colony of wabbler (wr) mice has been established at UCLA, and the genetic background of any mouse used will be known dozens if not hundreds of generations back. This strain manifests a neurological mutation in the form of cervical anterior horn cell degeneration, the mutation is autonomic recessive, and heterozygote. Normal homozygote animals will be used in this study. Thus far, no alterations in neurons from such animals have been found which might obscure the proposed program. The wabbler mice have been thoroughly studied electron microscopically, therefore we do not believe the wabbler trait will affect the validity of the proposed study and if such occurs we feel certain that we will recognize it. In any case the relation of aging to this spontaneous degeneration in this mouse colony should be of additional interest.

In summary, the possible disadvantage in using this colony of mice is outweighed by the opportunity to do the proposed study in a genetically controlled and homogeneous population, and the fact that these mice age rapidly. (They are fertile after six months of age, and oldest in the colony, 18 months, appear to be becoming senile.) There will be a virtually unlimited number of animals available for the study. Some of these animals will be taken at selected ages and reacted for acid phosphatase in neurons for electron microscopic study; others will be irradiated for comparisons with the normal aging series, and with a relatively large backlog of materials to be studied and information already gathered in an extensive series of alpha particle irradiated animals.

The principal effort at first will be concentrated on examination of the central nervous system of a series of mice from fetal to senile from the following regions: lumbar and cervical anterior horn, cerebellar cortex, cerebral cortex and cerebral white matter. On the basis of this study, appropriate ages for irradiation and alkaline phosphatatase studies will be related and additional experiments suggested by the first series of observations will be designed.

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Age-Related Differences in DNA and Deoxyribonucleoprotein

It has been reported by several investigators that cellular aging is accompanied by an altered capacity to synthesize DNA, RNA, and protein. Recent advances in nucleic acid fractionation and assay techniques make it feasible to look for the cause of these changes at the level of the primary information carrier DNA. Changes in gene function might be expected to result either through alteration in structure or through failure of regulatory mechanisms at the gene level. Therefore we have studied DNA structural changes by hybridization techniques and DNA function in a DNA-directed cell-free system for protein synthesis. We have studied DNP (deoxyribonucleoprotein) structural changes by spectrophotometric and ultracentrifugal techniques and by electrophoresis on polyacrylamide gels. The template activity of DNP in the RNA polymerase system is also being studied.

Our earlier work suggested that differences in DNA isolated from young and old mice could be detected by measurement of the thermal denaturation of melted and reannealed samples. DNA from old mice displayed a higher percent hyperchromic shift than its young mouse counterpart. However, this effect was quite variable, and other methods were sought to examine these differences. It had been reported by Walker and McLaren (1965) that denatured mouse DNA may be fractionated by hydroxylapatite chromatography into at least two components, a large peak of single-stranded DNA and a smaller DNA fraction of presumably double-stranded character. This technique appeared to offer possibilities for examining differences in the secondary structure of DNA. The work of Bolton and his co-workers (1964) at the Carnegie Institution of Washington and of Martin and Hoyer (1966) suggested that the stability of the secondary structure of reannealed DNA is dependent upon the reannealing temperature. We have therefore studied the chromatographic behavior of sheared and melted mouse DNA on hydroxylapatite columns at various reannealing temperatures.

These studies have led to the fractionation of young and old mouse DNA samples into a number of fractions at various salt concentrations. Under these conditions, age-related differences are found. At an incubation temperature of 50°, for example, the 0.03 M fraction from 12-month-old mice is retained on the column whereas its 2-month-old counterpart elutes immediately. These differences are most pronounced for DNA samples high in residual protein prepared by a modification of the detergent technique of Kay, Simmons and Dounce. Generally, DNA from young and old mice behaves similarly whereas that from mature animals appears quite different. These differences are much less apparent in DNA samples containing less residual protein prepared by the Marmur method. Of greatest interest is the observation that the greater removal of protein by the Marmur procedure leads to decreased retention of partially reannealed mature mouse DNA on hydroxylapatite whereas the same treatment leads to greater retention of DNA from both young and old animals. This suggests that the quality of bound residual protein is distinctly different in the two cases, a phenomenon which might be explained by the presence of more cross linking histone molecules in mature mouse DNA and more non-histone protein in DNA prepared from young and old animals.

Methods have been developed in this laboratory for studying base-pairing of DNA by means of spectra and the shape of melting curves. A significant result of this work has been to show that DNA helices one thousand base-pairs long have a base-ratio similar to that of the total genome of the cell. By these techniques it has also been possible to determine some of the physical characteristics of DNA from the hydroxyapatite columns. These techniques are also being applied to age-related changes in DNP, and to RNA.

Because of the apparent importance of the protein component associated with DNA in our previous studies, and because nuclear protein has been implicated by the work of Allfrey, Littan, and Mirsky (1963) and of Huang, Bonner, and Murray (1964) in the control of genetic transcription, we have also carried out studies of nucleoprotein stability and composition as a function of age, examining the thermal stability of brain nucleoprotein isolated from mice of various ages. It has been observed that the Tm of mouse brain nucleoprotein decreases from young to mature animals and thereafter undergoes a gradual increase to thermal stabilities comparable to those of the nucleoprotein of very young mice. Protein content of the nucleoprotein preparation has been found to follow a similar pattern, decreasing toward maturity and increasing with old age. Recently, it has been observed that the histone content of isolated DNP remains relatively constant during age, but that the non-histone components vary considerably. The very significant conclusion to be derived from this work is that the amount and also the

type of protein associated with nuclear DNA and RNA changes in the course of aging.

Possible differences in mouse liver nucleoprotein from young and old animals have also been examined by means of sucrose density gradients at various ionic strengths. It was reasoned that gradients should isolate the various DNA and DNP and RNP species on the basis of molecular size differences and reveal the number of species of each existing at a given salt concentration. In theory, nucleoprotein, after its point of minimum solubility in 0.12 M NaCl, begins to dissociate as the ionic strength is raised. While it is generally agreed that all histone is dissociated from DNA at 2.6 M salt, the recent report of Georgiev, et al, (1966) indicates that all operable template sites are "opened up" or freed from protein interaction between 0.4 and 0.6 M NaCl. We are determining what species of DNA and DNP are present at the critical points of dissociation and investigating any variations that these different species exhibit in their template activity in an in vitro RNA polymerase system. Concomitantly, we are comparing the behavior of nucleoprotein from young, mature, and old animals when subjected to sucrose density gradients and also comparing their polymerase template activity.

These various studies indicate that structural and functional differences exist in the composition of mouse DNA and deoxyribonucleoprotein as a function of age. The goal of our laboratory is the elucidation of the detailed nature of these changes as a possibly critical step in the solution of the problem of senescence.

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Wood Veterans Administration Center
Wood, Wisconsin

Performance on a Motor Steadiness Battery as a Function of Chronological Age with Older Normal Domiciliary Members

Neuropsychological test batteries are now in common use and make a definite contribution in the diagnosis of central system diseases. One section of the neuropsychological test battery involves the assessment of motor functioning. These tests permit decisions on the presence or absence of diffuse or lateralized lesions and on the functioning of extra pyramidal and cerebellar systems. At present we do not have adequate normative data for these tests on an older population. It is the purpose of this study to develop normative data on older Domiciliary members who are without history of psychosis or brain damage.

The tests employed include the Dynamometer (measuring grip strength in kilograms), the Grooved Pegboard (involves placing grooved pegs into grooved slots, a measure of fine manipulative speed and coordination), Finger Oscillation Test (number of oscillations of a fore finger in ten seconds, Foot Oscillation Test (number of foot oscillations in ten seconds), and Maze Test (measures ability to move a stylus through a maze without touching the sides), Grooved Steadiness Test (measures ability to move a stylus through a straight maze and back to point of origin without touching the sides; performed in a vertical direction and then in a horizontal direction), a Steadiness Test (requires that one hold a stylus for ten seconds in openings varying in size and attempting not to touch the sides of the openings; this is performed in two ways: with the arm unsupported and with the arm resting on the table). All tests are performed first with the dominant limb and then with the nondominant limb. The last half of the series starting with the Maze Test have both the number of touches and total length of time of touches recorded. In addition to the above tests the Information and Similarity Verbal subtests and Block Design and Picture Arrangement performance subtests of the Wechsler Adult Intelligence Scale were administered in order to get an estimate of intellectual functioning. Subjects for the study had to meet the following criteria:

A. No history of brain damage
B. No history of psychosis
C. No current confusion
D. Testable
E. No positive signs of neurological examination
F. Age 55 years and older.

The data are in the process of being analyzed.

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Psychoacoustic Parameters of Presbycusis

The common causes of hearing deterioration as a function of age are the vascular and neural changes accompanying the aging process, yet information concerning the psychoacoustic parameters is relatively sparse. This information is especially lacking in age groups over 60 years of age when epithelial and neural atrophy have been shown to be maximal (Schuknecht). Neither has much information been available regarding the relationships between auditory perception, discrimination, recall and all the psychological factors attending presbycusis and related structural changes (Davis and Silverman).

A recent report by this investigator of a factor analysis of hearing and psychological characteristics of men over 65 years old indicated that age emerged as an isolated factor. Pattterns of hearing deterioration as a function of age failed to show the continued regression of hearing levels anticipated from the few available reports. Of the eight factors that emerged from the principal components factor analysis of 47 variables of which measurements were taken, none of the psychological and of the physical complaint variables was related to the reduced hearing levels of the 137 geriatric subjects tested.

At the present time there is no acceptable way of estimating the significance of sensori-neural losses in aging populations, and therefore no technique for evaluating the use of prosthetic devices for presbycusic patients. Besides the many theoretical questions to be answered by this type of research, the practical value has been stated by the Council of the American Medical Association: "A method more satisfactory than those now in use is needed to evaluate hearing losses in terms of the disability they produce." The problem of this study is to describe experimentally the relationships between auditory perception of non-language sounds and language comprehension as a function of aging.

A psychoacoustic analysis of the aging auditory system is necessary to adequately describe changes in perception, attention, memory and comprehension in terms of phonemic and linguistic regression.

It is planned to provide complete audiometeric testing to all patients over 65 years being admitted to the Domiciliary at the Veterans Administration Center in Los Angeles. In order to identify diagnostic categories for establishing presbycusic norms in the age groups above 65, the following tests will be administered:

1. Complete medical evaluation
2. Psychological test battery
3. Pure tone discrimination
4. Short increment sensitivity index test
5. Bekesy Audiometry - sensory-neural acuity level
6. Alternate binaural loudness balance
7. Speech audiometry - SRT and percent discrimination
8. Calibrated auditory test for recent memory
9. Tone decay test
10. Rhyming test (Fairbanks)

Prior to investigating behavioral changes of the auditory system in an aging population, threshold levels for pure tone perception had to be established. The pure tone audiograms of 145 veterans 65-75 years old previously reported by this investigator (Sklar 1962) contributed some information to this neglected area of study. An extended sampling is necessary, using more refined equipment and better stimulus controls. In another study by this investigator, "Some Relationships Among Psychological Test Scores, Language Disturbances and Autopsy Findings in Aphasic Patients," the deterioration of the relation between auditory perception and auditory comprehension indicated a possible methodology of analyzing the progression of auditory verbal agnosia that may accompany presbycusis.

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The Effect of Varying Signal-to-Noise Ratios on Speech Discrimination Ability as a Function of Age

During the past several years the effect of aging on the hearing process has become increasingly important. The aged population, medico-legally defined as those persons of age 65 and over, is growing at an increasing rate with each subsequent year. According to the Department of Health, Education and Welfare, more than 17 million were in this age group in the United States in 1963, and by 1980 the Department projects that there will be 24 million. In 1959 the Metropolitan Life Insurance Company estimated that in the age group 64 to 74 approximately 129 persons per 1000 have some degree of hearing impairment, and in the age group 75 and above about 256 persons per 1000 have a hearing impairment. Based upon these figures Alpiner conservatively estimated that "...there are now over one million aged persons with impaired hearing, and that by 1980, there will be more than three million." Because such a significant segment of our aged population suffer hearing losses, the need to learn more about the effects of aging on the hearing mechanism is important from an etiological as well as a rehabilitative point of view.

Studies of the effect of aging upon general performance have for the most part dealt with the slowing and the reduction of effective behavioral capacity. For example, measurements of reaction and movement times have shown that "...the times required to execute simple movements tend to be greater than those for simple reaction times, but less than those for more elaborate choices".

Until recently, before the results of more recent research on changes of performance with age were available, it was generally assumed that slowing with age resulted primarily, if not entirely, from a breakdown of the peripheral mechanisms, i.e., the sense organs and/or the effectors. These mechanisms are still recognized as significant in slowing with age, as is shown particularly in experimental work done with vision. Welford, in discussing ocular changes that occur with age, suggests that "... although age changes in peripheral organs are unlikely to reduce signal strength to an extent that would lengthen simple reaction time, they might perhaps do so to an extent that would impair performance at more complex visual tasks: although gross outlines may still be clearly seen, finer details, which may be crucial, might cause difficulty".

However, Birren and Botwinick have shown that slowing in rate of conduction by peripheral nerves cannot directly account for more than a small fraction of the increase of reaction time with age, since there are a much greater number of fibers which are larger in peripheral mechanisms than in those which are more central. The larger nerve fibers are capable of greater speed of impulse transmission than the smaller fibers and thus, on a percentage basis, the smaller fibers are more affected by aging than the larger.

Therefore the smaller and more centrally located nerve fibers play an important role in determining performance in aging and account for much of slowing of reaction time with age. A possible change with age of dendritic potentials has been suggested as contributing to the slowing of the impulse conduction rate.

Of particular interest in the consideration of auditory sensory performance in aging persons is the phenomenon referred to by Welford as "neural noise." He suggests that we "...consider central processes in terms of 'signals' from sense organs to the brain and from one part of the brain to another being disturbed by 'neural noise' produced by random background neural activity or by irregularities in the action of the cells carrying the signals. The effectiveness of the signals will depend on the signal-to-noise ratio. This may be impaired by either a reduction in signal strength or an increase in the noise level". He suggests and discusses several factors which he believes could affect either signal strength or signal-to-noise ratios, or both: (1) a reduction in the number of functional cells, which, it would appear, could be either central or peripheral, or both; (2) an increase in random neural activity, suggested by some as evidenced by the increase of tinnitus oft-times found in older people; (3) longer

after-effects of neural activity found in older subjects which would have a confusing effect on subsequent signals and which would therefore effect continuous tasks more than discontinuous, a distinct factor in short-term memory; and (4) an activation, arousal, and autonomic activity wherein impulses to the cortex seem to have a facilitating effect, but if they reach very high levels of activation have an adverse effect by causing cells to fire spontaneously, creating "noise" in the system, as well as having so many cells in refractory that relatively few will be left to carry the signal.

Most of the audiological work done in presbycusic research has dealt with pure tone thresholds. However, it is a well-known clinical observation that the intelligibility of speech for presbycusic persons is seriously affected. Speech discrimination scores are very frequently much poorer than would be expected by either the testee's pure tone test results or his speech reception threshold. The term "phonemic regression" was coined by Gaeth to describe this phenomenon.

Various attempts have been made to explore and explain this phenomenon of hearing deterioration in the aged. Bordley and Haskins, Finzi and Calearo and Lazzaroni studied the effects of varying the time parameter of speech through the use of accelerated speech tasks. Jerger et al describes the use of the short increment sensitivity index (SISI) test with various age groups. Loudness recruitment has purportedly been investigated by various means, i.e., de Bruine Altes by means of the monaural masking-, the hearing span-, and the index vocalis method; Jerger and Meurman used difference limen for intensity (DLI) measures; Pestalozza and Shore and Goetzinger et al used Reger's monaural loudness balance test; Krejci and Fischer used Luescher and Zwislocki's "Unterschiedschwelle" test; and Van der Waal used Mol's dynamogram to test recruitment.

Excessive tone decay in elder persons was examined by Goetzinger et al and Rosen et al. Abnormal differences in discrimination ability between an easy test, such as the C.I.D. W-22, and a difficult test, such as the Rush Hughes recordings of the Harvard P.B. lists, has been explored by Goetzinger et al and Harris et al.

Koenig and Ross et al studied pitch discrimination as a function of age. Feldman developed a "dichotischer Diskriminations test" (d D test) to study dichotic presentation of speech stimuli to various age groups, including the aged. Matzker and Springhorn studied directional hearing as a function of age, and Matzker employed a binaural fusion of filtered speech, also as a function of age.

All of these approaches have, to one degree or another, shed additional light on the hearing problems of the aged. However, an area suggested by the neurophysiological implications discussed earlier, which as yet has not been studied, is that of the relationship of various signal-to-noise ratios on speech intelligibility as a function of age. It is therefore hypothesized that: (1) there will be a decreased resistance to signal interference by external noise as a person gets older; (2) this lessened resistance could, in part, be responsible for the poorer discrimination ability, or the so-called "phonemic regression syndrome"; (3) decreased speech discrimination ability can and does occur in the aged independently of hearing sensitivity for pure tones or of speech reception thresholds.

To test these hypotheses a research study is being prepared wherein three groups of subjects will be studied: (1) young "normals," (2) old "normals," and (3) old "presbycusics." Standardized speech discrimination tests and procedures, applying various signal-to-noise ratios, will be used. Percent correct response will be the criterion measure, and error responses will be analyzed and studied.

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Age-Associated Changes in the Skin and their Systemic Metabolic Equivalents

Project I

The skin may serve as a mirror of systemic metabolic events. We have been particularly concerned with the response of the skin to nitrogen-losing states from the point of view of (1) developing techniques for estimating degree of nitrogen loss in debilitating conditions such as following surgery, chronic disease, and in aging, and (2) explaining reduction of mucopolysaccharides in this organ which occurs with age.

In an earlier study (Sobel et al. Am. J. Phys. 212: 773, 1967) loss of hyaluronic acid, chondroitin sulfate and extravascular albumin from the skin during starvation in mice was investigated. Now the loss of hyaluronic acid (ΔHAH) and chondroitin sulfate (ΔCSH) have been correlated with loss of nitrogen (ΔN) as follows:

$\ln \frac{\Delta HAH}{N} = 3.52280 - 0.74516 \ln \Delta N$, $r = .799$, $p < .001$. $\ln \frac{\Delta CSH}{\Delta N} = 2.88043 - 0.84072 \ln \Delta N$, $r = .704$, $p < 0.01$. Thus $\frac{\Delta HAH}{N}$ and $\frac{\Delta CSH}{N}$ is greatest for small losses of nitrogen and decreases as Δ N increases. This is thought to be related to reduced rate of synthesis of fibroblast-produced substances during starvation in order to conserve materials and energy stores and to release of protein present in the ground substance. The latter is consistent with the concept that the ground substance in a limited sense may serve as a protein storage site. The findings suggest a very sensitive feedback system to conserve protein in more vital organs. However, the extent to which mucopolysaccharides may be depleted appears to be limited, suggesting either that the materials now have different metabolic characteristics or physical attributes compared with the material lost earlier, or that their presence is necessary for life to continue.

This has led us into the study of factors which control the polydispersity of hyaluronic acid, molecular weights, and turnover rates. We are also asking whether an explanation of the reduction in the mucopolysaccharide content of skin with age may not lie in the changes which take place in these consituents during nitrogen loss. Included in this study is the question whether any irreversible changes result in the skin from the period of starvation.

We had previously observed changes in the characteristics of hyaluronic acid known as its "domain." When albumin was allowed to diffuse into and through membranes containing hyaluronic acid, less was retained and more passed through the membranes when the hyaluronic acid was derived from the skin of starved animals compared with their controls (Sobel et al. Amer. J. Physiol. 212: 773, 1967). This was also true when material was derived from older dogs compared with younger animals. In fact, in this latter situation log albumin passed = 1.8336 + .0069 x age ($r = .63$, $p < .01$) and log albumin retained = 1.90006 - .0048 x age ($r = .52$, $p < .01$) (Sobel et al. Proc. 7th Internat. Congress of Geront.). We are, therefore, now investigating hyaluronic acid from the skin of animals which had been starved and re-fed in order to acquire information on the subsequent characteristics of this substance. It is noteworthy that changes which occur in hyaluronic acid with age and as a result of starvation have definite similarities.

Incidental to studies with hyaluronic acid in skin was the demonstration that labeled albumin enters the extravascular space in at least two rates in accordance with the concept of Gersh and Catchpole that the ground substance of connective tissue consists of a water-rich gel-poor phase and a water-poor gel-rich phase (Sobel et al. Proc. Soc. 123: 519, 1961). Although this terminology is unacceptable, it is thought that the faster rate is related to flow, to a limited extent, and to diffusion into the phase which is free of or low in hyaluronic acid, and the slower rate to the domain of hyaluronic acid.

We have already demonstrated that clearance of labeled albumin from the blood and transvascular passage into the interstitial space of the myocardium is decreased with age (Sobel et al. J. Geront. 19: 501, 1964) and that the latter is very likely related to decrease in hyaluronic acid content (Sobel and Hewlett, J. Geront. 22: 196,1967). We have also observed an increased amount of labeled albumin in the skin following estrogen treatment (Sobel et al. Proc. Soc. Exptl. Biol. Med. 119: 358, 1965) which is accompanied by increased content of hyaluronic acid (Sobel et al. Biochimica et Biophysica Acta. 101: 335, 1965). These studies, and others by us, related to our concern that changes in the composition and morphology of the ground substance of connective tissue may affect the rate of transfer of molecules to and from the cells.

Finally, in accordance with our initial plans, we are attempting to determine whether it is possible to correlate decrease in hyaluronic acid or chondroitin sulfate in the

skin of patients with nitrogen loss. Using an 8mm skin punch it is possible to isolate and measure these substances. In a study with Dr. J. J. Cincotti, Chief, Surgical Service. VAH, Sepulveda, we are comparing decrements in hyaluronic acid/collagen and in chondroitin sulfate/collagen in samples taken during surgery and when realimentation is initiated, with nitrogen loss. Preliminary studies suggest that this approach is justifiable.

Project II

The changes which take place in exposed human skin with age differ in a number of ways from those which occur in the covered part of the body. In exposed skin, changes occur in the morphology and staining characteristics of collagen ("basophilic degeneration") and apparent accumulation of substance which stains like elastin ("senile elastosis"). There is a great deal of debate whether this is indeed elastin or altered collagen. In addition, an increase in hyaluronic acid has been reported. This subject is of considerable interest to this laboratory for a number of reasons, (1) the obvious -- clinical-cosmetic problem and its control, (2) the possibility of collagenolysis, (3) the possibility of distortion of molecular configuration resulting in change in staining characteristics and morphology, (4) the possibility of elastinogenesis, and (5) increased hyaluronic acid in contrast to a decrease with age in unexposed skin.

We intend to investigate the problems seriously and have been exposing hairless mice to ultraviolet light.

Project III

We have been concerned with the possibility that prolonged exposure to oxygen at high partial pressures may induce changes which occur normally with age. Some age-changes are thought to result normally for accrual of effects of free-radicals arising from normal metabolism and external influences (Harman). It is known that oxygen poisoning may produce some of its effects by the formation of oxidizing free-radicals, associated changes may be effects on certain enzymes, formation of H_2O_2, lipid peroxidation, crosslinking, oxidation of various sorts, etc.

We have particularly asked whether changes are produced in the connective tissue constituents of skin of animals exposed to hyperbaric oxygen and whether any changes which occur are similar to those observed in the skin of older animals. There are at least four areas in which high pressure O_2 may effect the composition of the connective tissue,

(1) hydroxylation of the proline-rich precursor of collagen (Juva et al. 1966, Udenfriend 1966), (2) crosslinking of collagens, (3) fluorescence of elastin and collagen (LaBella, 1966), and (4) depolymerization of hyaluronic acid (Pigman, 1963) (Meyer et al. 1960). In addition, there is the overall effect on energy metabolism and protein metabolism in particular. Mice are exposed to a 27% - 73% oxygen-nitrogen mixture at 45 lb. pressure (relative) for 72 hour periods in an hyperbaric chamber. They are then maintained under normal conditions for 96 hours and the cycle is repeated. Mice have been exposed for 26 periods of compression. The skin is removed for studies in the collagens and mucopolysaccharides. In the former, usual soluble collagens are measured and evidence of increased crosslinking and oxidation is sought. In the latter, the quantity of molecular weights of hyaluronic acid chondroitin sulfate are studied.

Project IV

The carcasses of C57 BL/6 Hb mice between 1-2 years of age were analyzed for N, Ca, K and formed-creatinine (presumably derived from creatine phosphate) by a procedure previously described (Sobel and Hewlett, Proc. Soc. Exptl. Biol. Med. 126: 149, 1967). Between 1 year and 2 years female mice lost no weight, lost 2.2% of body nitrogen, 15.5% of body calcium and 1.5% of creatine phosphate, while males lost 12.6% of weight, 14% of body nitrogen, 28.5% of calcium and 23.3% of creatine phosphate. This surprising display of female superiority coincides with the mortality data which is 2% and 20%, for both sexes, at 1 and 2 years, respectively, but is 86% for males and only 46% for the females by 2½ years of age.

The above, along with ongoing work is intended to shed light on --

Project I

(a) the factors which influence polydispersity of molecular weights of hyaluronic acid; (b) the question whether age-changes in the content and the physical properties of hyaluronic acid in the skin may influence passage of molecules through it; (c) determine how estrogen may affect the above; (d) determine whether the loss of hyaluronic acid and chondroitin sulfate in the skin correlates with nitrogen loss in man as it does in mice.

Project II

The changes which occur in the connective tissue of skin following chronic exposure to ultraviolet light.

Project III

The changes which occur in the skin following prolonged exposure to hyperbaric oxygen.

Project IV

Some of the reaons for sex differences in mortality and morbidity.

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Effect of Radiation on Aging, Protein and Nucleic Acid Synthesis

In recent years the concept has emerged that "aging" in animals can be induced by ionizing radiation. This view has gained support experimentally. Kohn and Guttman, 1963 and Jones and Kimeldorf, 1964, for example, have demonstrated that the lifespan of mice or rats exposed to a single dose of ionizing radiation is foreshortened when animals are exposed at an early age.

The precise effects of radiation in living systems are not known, although a large body of evidence points to alterations in the genetic material as being a primary effect. Undoubtedly, other vital components of the cell are also affected, especially the nuclei acid components of the protein synthesizing system such as ribosomal, transfer and messenger RNA. Alterations in DNA, due to radiation have been observed and could affect the synthesis of "proper" proteins since coding of the proteins is believed to be dependent upn the correct sequence of triplets in the DNA. In support for these ideas, Van Lancker, 1960 and Boudnitskaya, et al., 1964 demonstrated that exposure to X-irradiation lowers the rate of DNA and RNA synthesis in tissues and Wulff, 1961 observed a decrease in the rate of RNA synthesis in aged mice.

Thus, studies concerned with the effects of ionizing radiation on the synthesis of nucleic acids and proteins should be of fundamental significance in gaining an insight into the

mechanism of aging in animals. For this purpose, two widely divergent biological systems have been selected for detailed investigation: 1) the developing chick embryo because of its comparatively high radio-sensitivity and 2) the protozoan Paramecium aurelia because of its unusually high resistance to ionizing radiation.

Several aspects of protein synthesis in control and irradiated animals are being investigated. Steps involved in this process amenable to study are: a) activation of amino acids, b) transfer of activated amino acids to the ribosomal site, c) radiation effects on messenger RNA production and d) radiation effects of ribosomal RNA and its subsequent role in protein synthesis. Some experiments involve comparing in vivo uptake of selected C^{-14} labeled substances into proteins and nucleic acids of subcellular fractions of control and irradiated tissues. Other experiments are directed primarily toward pinpointing the site (or sites) within the cell which may have been affected by ionizing radiation. Various subcellular fractions of irradiated tissues are replaced with corresponding fractions of unirradiated animals and compared in vitro for amino acid incorporating activities.

Preliminary studies carried out thus far in which groups of 3 and 12-day old embryonic chick eggs were exposed to LD_{50} dosages of x-rays revealed few, if any, detectable changes in the gross physical and chemical characteristics of both DNA and RNA isolated from the breast muscle of survivors on the 17th day. In addition, physical and enzymatic properties of the contractile protein myosin, isolated from the breast muscle of irradiated animals did not differ significantly from those of unirradiated controls. It has been observed, however, that the RNA/protein ratio of the breast diminishes more rapidly from the 12th to the 19th day of development in irradiated animals than in controls. Of interest in this respect is that the RNA/protein ratio in the adult breast decreases as a function of age.

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Biosynthesis of Glycosaminoglycans and Aging in vitro and in vivo

It is well documented that the glycosaminoglycans (acid mucopolysaccharides) change both qualitatively and quantitively during maturation and aging and that these changes can be directly related to the pathology of aging in connective tissues. These lesions appear in blood vessels, kidneys, lungs, bones, and joints of the aged.

There are several different glycosaminoglycans which, associated with protein, form the ground substance of connective tissues. These polysaccharides are all produced by connective tissue cells all of which are derived from mesoderm.

We are studying the biosynthesis of these glycosaminoglycans in cells grown in well defined culture media and in vivo in animals of different ages.

It has been shown that normal mammalian cells grown in culture are not immortal but that they pass through some fifty generations during which time they mature, finally cease to divide and die. This appears to be a genetically programmed aging process which results in the aging phenomena in the multicellular organism.

Cells obtained from tissues of embryos obtained by caesarian section are isolated to develop strains of cells derived from a single connective tissue cell. These normal cells remain in the diploid state in culture; that is to say, they possess the normal number of chromosomes. Some cell strains however develop chromosomal abnormalities and become cell lines. These cell lines do not age and appear to multiply indefinitely in tissue culture and are analogous to cancer cells.

These cells, both normal and abnormal, remain viable in the frozen state when the freezing conditions are carefully controlled. Therefore, it is possible to arrest aging at any time during a culture's lifespan and to restart the process by thawing and reculturing the cells. In these studies, we measure the changes in biosynthetic processes of fibroblasts and chondrocytes derived from the same parent cells at different times in the cell strain's lifespan, but measured at the same time and under identical conditions.

These connective tissue cells, synthesize the sulfated glycosaminoglycans, hyaluronic acid and collagen. The measurement of biosynthesis is followed chemically and by the use of radioactive precursors. Cell growth and differentiation are followed by measurement of deoxyribonucleic acid, protein, and by chromosome counting.

Another aspect to consider in aging of a mammalian system is the relationship of the cell to its environment. As an animal matures, a number of changes occur which are known to have a direct effect on cells. Blood levels of hormones and nutritive factors are examples of these changes. In order to evaluate these factors, cells grown in culture to different age levels are transplanted into animals of different ages using semipermeable membrane chambers. These cells maintained in vivo in their natural biological milieu, are removed after long intervals and are then assayed for biosynthetic activity.

These techniques provide a valuable approach to a number of problems of aging. These include the identification of cell types associated with synthesis of glycosaminoglycans, the cellular location of synthesis and the relationship of these processes to their environment and differentiation under controlled conditions upon which hormonal, nutritional, and pharmacological changes can be superimposed.

From these studies it should be possible to understand why connective tissue changes with age and time relationships between age and the incidence of cardiovascular disease, osteoarthritis, glomerular sclerosis and malignancy.

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Bone Tissue Metabolism as Influenced by Aging Factors

The loss of bone tissue as a consequence of aging is a well-documented occurrence. The negative calcium balance, which generally starts sometime during the fifth decade, is a gradual, continuing process and may culminate in the development of senile osteoporosis. Just why this loss occurs has not been explained satisfactorily. It is obvious that bone resorption exceeds bone formation; but whether this is due to an increase in the rate of resorption or to a slowing of the formative processes with no change in rate of resorption has not been resolved. Whatever the cause, it seems probable that a change in bone cellular regulation is involved.

Osteoporosis can be the result of a number of factors including that type developing in individuals with Cushing's Syndrome. Similarly, the continuous administration of glucocorticoids leads to this condition if preventative measures are not taken. Thus it is apparent that an excess of these particular hormones is associated with a net loss of bone tissue. The overall aim of this project is to investigate the possibility that the adrenal cortex secretions are implicated in the subtle loss of bone tissue during the aging process.

In addition to the glucocorticoid fraction, ascorbic acid secretion from the adrenal cortex will also be considered. This compound is of interest because it is known to be involved in bone formation, results from this laboratory indicate that it may be involved in bone catabolism, and recent results (J. Clin. Nutr. 20:799) illustrated that osteoporosis develops in siderotic individuals. The characteristic pattern of adrenal secretion in

response to stressful stimuli is also of interest. In response to adequate stimulation the adrenal cortex first releases ascorbic acid, and after a lag period of 15-30 minutes the hormones are released to the circulation. The physiological significance of this sequence of events has not been clarified, although it does not seem that the ascorbate release is related to the biosynthesis or transport of the hormone.

Of further interest is the observation which indicates that adrenal cortical ascorbic acid concentration decreases with age, reaching a low point about the time that bone tissue loss is initiated. The specific aims of this project are to investigate the possible interrelationships between these two products of the adrenal cortex as they influence connective tissue, particularly bone tissue. Questions of immediate interest include: Does the characteristic pattern of adrenal cortex secretion in response to corticotrophin (first ascorbic acid, next glucocorticoid) have some bearing on skeletal metabolism? In older age, when the adrenal cortex ascorbic acid concentration drops, is less ascorbate released for a given amount of stress? If so, does this changing ratio of ascorbate to glucocorticoid hormones influence bone tissue? In short, does adrenal cortical secretion influence skeletal metabolism, and are its activities which may change with age implicated in bone tissue loss and the development of senile osteoporosis?

Results to date have shown that weanling rats respond to ACTH injection in the following manner: Bone Ca^{45} (given 96 hours prior to the ACTH) is mobilized within 1 hour as evidenced by a highly significant increase in serum Ca^{45}. This significant elevation remains until 8 hours post-injection when the trend towards normal starts. Adrenal ascorbic acid levels are initially decreased (40%), remain low for 4 hours, and exhibit an overshoot at 24 hours in reaccumulation. Older animals (9-10 months) do not exhibit as great an increase in serum Ca^{45}, adrenal ascorbate decrease, or the potential to reaccumulate this compound in the adrenal following ACTH adrenal stimulation. Preliminary work using animals up to 16 months old indicated that adrenal ascorbic acid concentration drops with age.

Young guinea pigs exhibited a Ca^{45} response to ACTH similar to young rats. Adrenal vitamin C also decreased significantly but did not reaccumulate in a manner similar to young rats. This difference may have resulted from a decreased feed intake following injection of the hormone. Results with guinea pigs ranging from weanling to approximately 12 months of age suggest that, similar to the rat, adrenal ascorbic acid concentration decreases with age.

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Follow-Up of Aged Patients Who Undergo Surgery

The aged patient has always been known to have an increased risk during surgery for a great variety of reasons. Dr. Tice is not only following all aged patients who undergo surgery at this hospital and keeping accurate records as to their course relative to complications, morbidity, mortality, etc. but is also conducting a study in which he hopes to be able to improve their postoperative morbidity and mortality.

It has been observed by Dr. Tice and the surgical staff that preoperative blood urea nitrogens and simple urine analysis are deceptive in the evaluation of the aged patient for surgery. Elderly patients with normal or relatively normal blood urea nitrogens and negative urinalysis often develop uremia postoperatively, which greatly complicates their course. Those aged patients who do develop uremia often do so after a period of dehydration and oliguria during or immediately after surgery. It has also been noted that creatinine clearances will more accurately reflect the aged patient's true renal status and those patients who have a significant reduction in creatinine clearance (under 80 ml. per minute) are given a regimen of intravenous fluid therapy, with or without mannitol, to maintain adequate renal plasma flow and renal excretory flow during surgery and in the postoperative period.

The preliminary observations of this method of management indicate that it significantly decreases morbidity due to uremia and other renal complications of the aged patient.

Harry Walter
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Differentiation of Young and Old Protein Molecules and Separation of Cells and Particles by Counter-Current Distribution

Little work has been done in the investigation of possible alterations or heterogeneities that arise in biologically occurring macromolecules as a function of their biological age. Research has been done on elucidating chemical alterations of collagen during aging, but this structural protein is a special case involving, among other things, the presence of some unusual amino acids. The aim of this research project is to investigate chemical

changes in the behavior of certain soluble proteins that occur as a function of the time that has elapsed since their biosynthesis. Such an alteration would, by some applied criterion, allow the differentiation of an older molecule from a younger one of the same species and may (but need not) affect the molecule's biological activity.

The availability of techniques for the separation of younger and older erythrocytes by centrifugation (e.g. Leif and Vinograd, Proc. Nat. Acad. Sci. U.S. 51, 520 (1964) or of their lysates by a serial osmotic hemolysis procedure (Simon and Topper, Nature 180, 1211 (1957)) first prompted us to use the red blood cell as a system to study. We have since developed an entirely new method for the segregation of different-aged red blood cells (counter-current distribution), which enables one to obtain red blood cells which differ in age by only a few days (Walter and Selby, Biochim. Biophys. Acta 112, 146 (1966)). Hemoglobin and erythrocytic enzymes of slightly different ages may be obtained in this fashion and analyzed. Specifically, this study will be comprised of the following:

In order to make maximum use of our finding that erythrocytes of slightly different ages can be separated by counter-current distribution, an attempt will be made to further improve this method. Procedures which spread the red blood cells over a large number of tubes in the extraction train, separate them completely from white blood cells, and allow larger amounts of red cells to be processed will be sought.

Hemoglobin and enzymes derived from young or old humans, horse or rat erythrocytes will be compared in a number of studies. These will deal with aspects of primary, secondary and tertiary structure. An attempt at finding the molecular basis for reduced enzyme activities in older red cells will be made. A preliminary investigation will be undertaken to determine when, in the lifespan of the red cell, a particular alteration in hemoglobin or an enzyme takes place. Since the counter-current distribution method allows us to differentiate cells of slightly different ages, this should be feasible.

Our marked success in separating red blood cells of slightly different ages by counter-current distribution has prompted us to test the apparent homogeneity of certain other cells (e.g. bacterial) and sub-cellular particles by examining their behavior on counter-current distribution. It is hoped that this technique will permit the further resolution of materials that appear homogeneous by the application of other criteria. Preliminary results (see below) are most encouraging.

Significance of this research

We have begun a study of the nature of chemical and structural alterations of erythrocytic proteins as a function of their biological age. Evidence has been obtained by ourselves and others that some alteration(s) in mammalian hemoglobin takes place in aging. This protein reacts to a different extent with chromium-51, changes its oxygen dissociation, its electrophoretic mobility and its chromatographic behavior as a function of its age. We have also obtained preliminary evidence that some erythrocytic enzymes display an altered electrophoretic mobility as a function of their age, a finding analogous to that reported for hemoglobin. It is hoped that the present study can elucidate the nature of the change or changes in hemoglobin and in the enzymes studied. An attempt will be made to determine the molecular basis and possibly also the sequence of events that leads to diminished enzyme activities in older red blood cells.

It may well be that the aging of macromolecules, in general, constitutes a factor to be considered in the solution of certain investigations dealing with heterogeneities of functionally and structurally closely related molecular species (e.g. "isozymes" known to be controlled by a single structural gene). The experiments outlined here, although for the moment restricted to a study of macromolecules contained in a cell with a distinct life-span, could lead to a greater understanding of the relationship between molecular age and molecular structure and function.

The resolution of apparently homogeneous (bacterial) cells and sub-cellular particles (e.g. ribosomes) may well offer an additional approach to the study of cells in different parts of their life-cycle and of aspects of protein biosynthesis.

Specific aims

My primary research objective is to investigate alterations or heterogeneities that arise in biologically occurring macromolecules as a function of their biological age. More specifically, certain soluble erythrocytic proteins derived from young and old cells will be examined for evidence of chemical changes. Such alterations should, by some applied criterion, permit the differentiation of an older molecule from a younger one of the same species and may, but need not, affect the molecule's biological activity.

It may well be, as mentioned above, that aging of macromolecules constitutes a factor to be considered in the solution of certain investigations dealing with heterogeneities of functionally and structurally closely related molecular species. I hope that these experiments will lead to an increased understanding of the relationship between molecular age and molecular structure and function.

The main research objective in the experiments on the counter-current distribution of bacterial (and other) cells and sub-cellular particles is to investigate possible heterogeneities that may be uncovered and that are not readily observed by use of other separatory methods (e.g. the resolution of a bacterial culture into cells in different parts of their life cycle).

Kuang-Mei Wang
Veterans Administration Hospital
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Relation of Age to Protein Synthesis and Enzymatic Activities

I. Introduction and Specific Aim

Aging is a process involving the complex changes in cells after a period of time. One of the pertinent cellular changes related to aging is protein metabolism. The possible and essential factors determining the process of aging in relation to the alteration of protein metabolism may be summarized as follows:

(A) "Error" in specific replication of proteins and nucleic acids: An "error" of synthesis would probably be the result of an alteration of genetic control caused by either an extrinsic or intrinsic influence. With increasing age there is evidence of an increase in the microheterogeneity of proteins which may be the result of "errors" in protein synthesis.

The promulgation of the somatic mutation concept of aging by Szilard (1959) and Failla (1958), as well as by others, carries with it the implication that surviving cells would elaborate proteins altered as to their amino acid sequence and content, steric configuration, formation of cross linkages or in other ways which would render them non-utilizable metabolically. The occurrence of age-related autoimmune phenomena reviewed by Blumenthal (1964), aside from their role in physiological alterations and disease, supports the concept of fundamental structural changes in proteins in old individuals. However, comparable structural changes in nucleic acid or nucleoprotein as related to aging have not been revealed.

(B) Change in the efficiency of enzymes with age: The catalytic efficiency of enzymes decreases during the aging process. This could be the result of many factors: a blocking of the active sites of enzymes, an alteration in their structure by the changes

of substrate and co-factor concentrations, etc. Indeed, experimental studies have shown that in tissues of blood serum of aged human and other animals some enzymatic activities increase, some decrease and others show no change. However, no evidence has been shown of the consequence of such changes.

II. General Approach

The above described possible and essential factors resulting from aging lead to some important lines of investigation regarding the alteration of protein metabolism:

The study of age-related alterations in certain important metabolic enzymes: The enzymatic activities of organs represent important parameters for characterizing their metabolic activities. Therefore, a study of such parameters would be pertinent to elucidate the biochemical events related to the aging processes. Moreover, since enzymes are proteins, alterations in their activities should reflect some change in their protein structure.

The present study will be concerned with the distribution of enzymatic activities in different cellular components of tissues at various ages of a given animal. Initially this study will investigate the enzymes involved in the three major pathways of carbohydrate metabolism (glycolysis, the pentose monophosphate shunt, and tricarboxylic acid cycle) and the inter-related amino acid metabolism. This study will show (1) the changes of cellular components during development and aging, and (2) the changes in distribution of enzymatic activities in these components.

A study of the effect of exogenous substrates, hormones, and ions, etc., on enzymes of developing and aging tissues will follow. Although it is necessary to investigate the factors involved in degeneration of certain metabolic functions of a given tissue in the study of aging processes, of equal importance is the understanding of developmental processes of the enzymatic activities concerned with the metabolic functions of such a tissue. Therefore, the information obtained from these parallel studies will establish the essential factors involved in aging processes. Such study will demonstrate (1) whether one or more agents are required to correct the defect and (2) at what ages and conditions the given agents are more effective..

The change of enzymatic activities has generally been assumed to reflect changes in metabolic function. Correlations between change in enzymatic activity and alteration of a given metabolic

function have not been clearly shown. A quantitative, perhaps qualitative, change might result from different rates of formation and degradation of the enzymes in growing and aging animals. By using radioactive amino acid incorporation study the rate of formation of the above enzymes will be investigated. Each enzyme will be isolated from a given tissue by the available methods and precipitated by its specific antibody. The radioactivity of the precipitate will be counted. A comparison of the rate at which the isotope is incorporated into the enzyme and at which the radioactivity of the enzyme diminishes in growing and aging animals will allow a calculation of the relative rates of formation and degradation of the enzyme *in vivo*.

A study of age-related alterations of protein synthesis: In the light of the current concept of protein synthesis studies of the ribosomal particles and the messenger RNA synthesis are necessary. These studies would involve looking for possible structural, functional and quantitative changes in the ribosomes as well as for possible changes in the nucleic acid metabolism.

It is well established that the mechanism of protein snythesis involves first the activation of amino acids. These are then transferred via transfer RNA onto messenger RNA-associate ribosomes. The final assembly of the amino acids into peptides takes place at this time. The correlation of enzymatic activities with incorporation of labelled amino acids *in vivo* during development, as described in the previous section, may parallel changes of steps in the protein synthetic processes. Such changes may be found in the amount of protein or in the structural variations of the many constituents involved in protein synthesis. For example, the levels of amino acyl synthetase (the transfer enzyme), tRNA, mRNA, or ribosomes may be different at various developmental stages; the molecular species of the ribosomes may vary; etc. The ribosomal particles in tissues of various ages will be isolated and characterized with respect to physical and biochemical properties, such as sedimentation species, amino acid incorporating activity, etc. These characteristics may then be compared with those of ribosomes from other tissues reported in the literature. Certain commonly occurring enzymes will be selected for the study.

Another aspect of this phase of investigation will be the study of nuclear RNA's in tissues of various ages. Since both messenger RNA and ribosomal RNA are believed to be synthesized in the cell nucleus, nuclear RNA prepared from tissues will be examined for possible changes. The preparation and fractionation of various nuclear RNA's will be carried out by phenol extraction in the presence of sodium dodecylsulfate at 4^{o}, 25^{o}, 55^{o}, and 80^{o}. These nuclear RNA fractions will then be examined by sucrose-gradient centrifugation.

To correlate the changes in enzymatic activities with protein synthesis: A preliminary study in our laboratory of the incorporation of C^{14}-leucine *in vivo* into various organ proteins during the development of the chick embryo has indicated that the rate of incorporation of the radioactive label is highest in the early stages of development. Following from these results initial studies will be made to carry out the isotopic incorporation *in vivo* in conjunction with assaying some of the enzymatic activities. The results of this investigation would ascertain whether changes in some of the enzymatic activities are correlated with protein synthesis.

III. Significance of this Research

The study of enzymes involved in carbohydrate metabolism and interrelated amino acid metabolism in the tissues at various ages will permit a correlation of the emergence of enzymes with the appearance and degeneration of physiological functions in different organs. The changes in enzymatic activities may then be interpreted on the basis of protein synthesis. Moreover, the administration of external agents such as hormones, substrates and ions might give information concerning the mechanism controlling the rate of formation of enzymatic activities.

Harold White
Veterans Administration
Little Rock, Arkansas

Arylsulfatase in Normal and Disease States
Cooperative Study - Morphologic Changes in Aging, An Autopsy Study. I. Endocrine System

Our research interest in the field of aging is centered on the possible role mucopolysaccharides (MPS) play in this area. Among the essential facts known about this basic relationship of MPS to connective tissue in old and young animals is that (1) there is a decrease in total MPS with advancing age and (2) that there is a decrease in the ratio of Hyaluronic Acid (HA) to sulfated acid MPS (CSA/C). Such ratios may also be altered by endocrine manipulation.

Changes in connective tissue MPS and aging may be further related when one considers some of the known functions of this family of compounds. In particular, they are apparently involved in what may be called, for want of a better term, the binding of water. This may be roughly measured in two ways. One, by noting the total amount of water rich in MPS and two, by measuring the rate of water loss during drying of these tissues. Tissues rich in HA generally hold more water but have higher rates of water loss, while tissue rich in CSA/C usually show lower water content but

lower water loss rates. This implies that the bonded structure of water induced by HA and CSA/C are different. This further implies differences in chemical activity between tissues containing less rigidly-bonded water structures compared to those in which water is in a highly-bonded state. This, in truth, would lead us to consider that in the aging process there is an increase in highly-bonded water and a decrease in biochemical activity.

Other known functional activities of MPS (heparin) relate to their lipid-clearing and anticoagulant activity. These latter two may be involved in the etiology of the atherosclerotic state, a degenerative process that is roughly correlated to the problem of aging.

Specifically, we have been looking to see if there is some indirect measure of MPS metabolism available. We have developed a test for sulfatase activity that we think may be related to the sulfation of MPS. Growth hormone is known to enhance the production of connective tissue, and in particular a so-called sulfation factor that is related to MPS metabolism. We have examined the serum for sulfatase activity in hypophysectomized animals to which we administered growth hormone. Some differences in sulfatase levels have been noted between control and experimental groups, but more should be done to test the significance of our results. It is our hope in the near future to perform assays of this enzyme in human serum to see if levels change with aging and/or degenerative diseases such as atherosclerosis.

In another area we have been studying lathyrism in the young dog to see if vascular lesions can be produced. Skeletal lesions, in particular those of the joints, have been readily demonstrable in our young animals. We have been particularly interested in the vascular lesions produced by Beta-amino-propionitrile (BAPN) since the ultimate changes in the elastic fibers and changes in MPS previously noted may be related to similar elastic changes seen in atherosclerosis.

One final phase of our study in aging is devoted to the role that the endocrine glands may have. A Cooperative VA study of autopsy material has been started to see if such a relationship obtains. Several hospitals are actively participating in this project, but proper funding for a wider participation has not been made available.

Shiu Yeh Yu
Veterans Administration Hospital
Jefferson Barracks, Missouri

Connective Tissues and Aging

In the program of Study on Connective Tissues and Aging, our investigation concerns a comprehensive project dealing with

histochemical, ultra structural and biochemical alterations in various connective tissues and their related structures with aging. It is also a study of influence of these connective tissue elements on the parenchyma of organs. The areas are as follows: (1) changes in amino acid composition of human aortic elastin with age, (2) biochemical, histochemical, and ultramicroscopic changes in elastic fiber in aging, (3) metabolic and immunopathological investigations of insulin.

Characteristic of the aging process is the replacement of parenchymal cells by non-functional connective tissue elements. In most organs this takes place in the form of replacement by changed collagen and ground substances with a lowered turn over rate. In the blood vessels the changes are even more complex, and little is known of the biochemical and biophysical processes by which the elastic fibers of these structures lose their resiliency. It has been contended by some investigators, that changes in elastic fiber are responsible for loss of resiliency and for the accompaning dilation of blood vessels, lung tissue or skin. Furthermore this is considered the first stage in the development of arteriosclerosis, pulmonary emphysema and wrinkling of skin by these investigators. Also, the proliferation of these connective tissue elements in the aged organs impairs the functions of parenchyma by increasing blood barrier or obstruction on the secretory pathway of the endocrines.

Another aspect of the characteristics of aging phenomena and arteriosclerosis in animals is the accumulation of calcium in the soft tissues especially in the aortic wall. Prevention and inhibition of the aging process and arteriosclerosis must rely on the knowledge of pathogenesis of the disease. This dystrophic calcification is seen in various instances including blood vessels, lung tissue of tuberculous necrosis, degenerating thyroid tissue, in areas of fatty degeneration and necrosis, in degenerated tumors and in many others.

From our studies, the aortic calcification initially appears approximately at maturation in the human. The characteristic calcification in the aorta primarily involves elastin of the aortic wall, contrasting to the other types of calcification which takes place on collagen fibers of bone and tooth. The structure and chemical nature of the pathologic mineral substance in aorta is exclusively a species of hydroxyapatite, which is similar to the mineral in bone or tooth. The evidence was provided by means of chemical analysis as well as x-ray diffraction studies on various human specimens. The crystalline structure has also revealed after the treatment with elastase; under an electron microscope the crystals are hexagonal, flat needle-shape and arranged topographically with non-sterically hindered crystalline ball with a

center of symmetry as of a pine-cushion. This crystalline apatite is initially nucleated on the regenerated elastic fiber of the aortic wall. Thereafter, the crystal continuously increases its size and number by the seeding effect of the preformed apatite. Consequently, this adverse growth of mineral causes the disorganization of the aortic wall and weakening of its structure.

It is well-known that the structural organization is significantly important in the aortic tissue. Our current ultrastructural studies have shown that on experimental aortic calcification induced by injection of epinephrine the initial change takes place at the junction area between elastic lamella and the smooth muscle. A replacement of this trauma by the connective tissue elements, such as, collagen, regenerated elastin and mucopolysaccharides, takes place as a tissue response and is followed by development of calcification in the wall.

For further investigations, the isolated elastic fibers from young and arteriosclerotic aortas are studied by an enzymatic disection. The macromolecular elastins have been partially digested with pepsin. The outer core of elastin has been isolated. From comparative studies of the outer core and the intact elastin with respect to chemical composition, amino acid composition and fluorescent substances, the characteristic age difference was observed primarily in the outer core of the fibers. Also, from the studies of amino acid composition, the characteristic change on aging of elastin was found in the primary structure of the protein. This finding is highly important from a genetical view point, since both young and arteriosclerotic elastin are synthesized by the fibroblasts of aortas. A specific protein in one lifespan alters its primary structure by aging or arteriosclerosis. This could be attributed to somatic mutation or a metabolic alteration of the young and old fibroblasts.

In order to elucidate this aspect, attention has been directed to the fundamental mechanism of development, differentiation and aging of the fibroblasts or the related cells of mesenchymal origin. Our current studies on differentiation of septal cells of lungs on developing rats indicate that the synthetic product of septal cells may vary within a lifespan of the cell during the differentiation. These data support the concept that alteration of the primary structure of elastin in one lifespan may be attributed to metabolic change of the old fibroblasts rather than mutation of the cell. However, if the post mitotic cell (the matured fibroblast) could further redifferentiate to another cell the mutation theory would be applicable for the explanation. The true mechanism remains to be determined.

Since therapeutic application of insulin in treatment of diabetes, there has been a steady decrease in the incidence of acidosis and coma and of death due to diabetic complications. On the other hand, among the diabetics there has been a progressive increase of frequency of vascular complications and of death which is attributed to diabetic angiopathies. Various investigators have emphasized the importance of lipid or free fatty acids or effect of mucopolysaccharides of serum or tissues in diabetes. However, whether these factors are causing or resulting from metabolic impairment of diabetes, is not clear. From the other aspect, diminution of action of insulin on the glucose tolerance of aged individuals is well known in the aging process. This can be attributed to one or more of the three factors (1) insulin antagonists, (2) impairment of synthesis or release of insulin, and (3) diminishing the response of insulin in target-organs of the hormone.

NIMH RESEARCH GRANTS

NATIONAL INSTITUTE OF MENTAL HEALTH
RESEARCH GRANTS
FISCAL YEAR 1967

GRANT NUMBER	INVESTIGATOR, PROJECT TITLE
MH 01981	Heinrich Kluver University of Chicago Chicago, Illinois Biological Mechanisms in Behavior
MH 04591	Eli Robins Washington University St. Louis, Missouri Brain Biochemistry in Manic-Depressive Disease
MH 06022	Barry Shmavonian Duke University Durham, North Carolina Factors in Autonomic Conditionability
MH 08060	Heinz Lehmann Douglas Hospital Verdun, Quebec, Canada Psychoactive Drugs in the Aged
MH 08061	Herschel Liebowitz Pennsylvania State University University Park, Pennsylvania Analytic Studies of Visual Perception
MH 08534	Robert Spitzer N. Y. State Psychiatric Institute Research Foundation for Mental Hygiene Albany, New York Evaluation of Psychiatric Status and History
MH 08556	Herman Buschke Stanford University Palo Alto, California Retention in and Retrieval from Immediate Memory
MH 10359	Stanley Samuels New York University New York, New York Biomedical Studies of Senile Dementia

MH 10895

Paul McHugh
Cornell University Medical College
New York, New York
Visceral Function in Affect and Brain Disorder

MH 10927

Irwin Feinberg
Research Foundation of State University of New York
Albany, New York
Sleep Patterns in Mental Illness

MH 11668

George Engel
University of Rochester
Rochester, New York
Psychological Determinants of Organic Disease

MH 12132

Chad Gordon
Age Center of New England, Inc.
Boston, Massachusetts
Personal Autonomy and the Social Processes of Aging

MH 12400

Aaron Antonovsky
Israel Institute of Applied Social Research
Jerusalem, Israel
Socio-Cultural Patterns and the Involutional Crisis

MH 12492

Barbara Anderson
California State College
Hayward, California
The Adaptive Tasks of Aging: A Psychosocial Analysis

MH 13434

Charles Eriksen
University of Illinois
Urbana, Illinois
Temporal Factors in Visual Perception Related to Aging

MH 13682

Robert Herrmann
Boston University
Boston, Massachusetts
Tissue-Specific DNA-Histone Interaction

MH 13821

Morton Kleban
Home for the Jewish Aged
Philadelphia, Pennsylvania
The Institutional Milieu of the Senile Patient

MH 14423

Charles Gaitz
Baylor University
Houston, Texas
Comprehensive Care of Suspected Mentally Ill Aged

MH 14832

Bernard Stotsky
Northeastern University
Boston, Massachusetts
Study of Mental Patients in Nursing Homes

MH 14881

Daniel Wilner
University of California
Los Angeles, California
Psychosocial Factors in Housing for the Aged

MH 14888

Esther Twente
University of Kansas
Lawrence, Kansas
Mobilization of Aging Resources for Community Service

MH 14889

Robert Kastenbaum
Mental Health Research Corporation
Boston, Massachusetts
A Training Program for Work with the Aged and Dying

MH 14893

Gertrude Hall
National Council for the Aging
New York, New York
Guardianship and Protective Services for Older People

MH 14894

Wilma Donahue
University of Michigan
Ann Arbor, Michigan
Milieu Treatment of Older Mental Patients

MH 14902

Walter C. McKain, Jr.
University of Connecticut
Storrs, Connecticut
Older Persons in Connecticut

MH 14915	Jeanne Thune Senior Citizens, Inc. Nashville, Tennessee A Study of Racial Attitude Changes in Older Adults
MH 14917	Jean Carey Community Service Society New York, New York Senior Advisory Service for Public Housing Tenants
MH 14923	Powell Lawton Philadelphia Geriatric Center Philadelphia, Pennsylvania Social and Medical Services in Housing for the Aged
MH 14924	Clark Blackburn Family Service Association of America New York, New York Social Work Team with Aging Family Service Clients
MH 14926	Barry Nathanson Hebrew Home for the Aged Riverdale, New York Workshop for Mentally Impaired Institutionalized Aged
MH 15020	Maurice B. Hamovitch University of Southern California Los Angeles, California Housing Needs and Satisfactions of the Elderly
MH 15047	Elaine Brody Home for the Jewish Aged Philadelphia, Pennsylvania Individualized Treatment on Mentally Impaired Aged

MH 01981
Heinrich Kluver
University of Chicago
Chicago, Illinois

Biological Mechanisms in Behavior

This research has been supported for 10 years and the investigator requested 5 year's additional support. The research will continue to be concerned with: (1) basic neural mechanisms in behavior, particularly with the behavioral, anatomical, and pathological changes occurring in non-human primates with temporal and limbic brain lesions of long standing; (2) the interrelations of brain and endocrines, with special reference to "spontaneously" occurring endocrine disorders in primates other than man; (3) the processes of aging in the nervous system; (4) the behavioral, physiological, and biochemical relations of metal-free porphyrines, with special reference to problems of psychiatry; and (5) an analysis of mescaline-produced behavior alterations, with special reference to changes in perceptual "similarity" criteria.

MH 04591
Eli Robins
Washington University
St. Louis, Missouri

Brain Biochemistry in Manic-Depressive Disease

This project is making postmortem biochemical studies of the brains of manic depressive patients and comparing them with "normal" brains. This investigation also includes a postmortem study of brain tissues from chronic alcoholics and from patients with senile dementia. These brains will be compared with those of aging persons who have died without mental disease. This investigation continues the research of the investigator into basic biochemical studies of the nervous system which appear to be relevant to the biochemical study of mental illness.

MH 06022
Barry Shmavonian
Duke University
Durham, North Carolina

Factors in Autonomic Conditionability

The investigator is measuring the physiological changes which take place in response to psychological factors, such as emotional

states. Individual and group differences which produce predictable effects have been demonstrated on the basis of personality types, age and sex. Emphasis is placed on exploring methods to reverse excessive physical reactions to emotionality. Data gathered and comparisons made among 26 young males, 17 young females and 25 aged males on conditioned autonomic and central measures, using EEG, GSR, plethysmograph and catechol amines, indicate both central and biochemical differences as well as peripheral factors such as arteriosclerosis, drying of the skin and disruptions in sweat gland activity are involved in the sympathetic reactivity of the aged subjects.

MH 08060
Heinz Lehmann
Douglas Hospital
Verdun, Quebec, Canada

Psychoactive Drugs in the Aged

This is a particularly unique work in geriatric psychopharmacology. Its aims are to develop rapid, reliable methods to evaluate psychoactive drugs in geriatric treatment, to determine specific behavioral correlates of the action of certain psychoactive drugs, to find those psychoactive agents which prove particularly safe and beneficial, and to develop predictors of therapeutic response of a particular patient to a particular drug. One hundred twenty psychiatric patients and 32 controls were administered single dose loadings of amobarbital sodium, methamphetamine hydrochloride, carbon dioxide with oxygen (inhalation), and physiological saline placebo, and tested before and after each drug administration on a psychophysical battery of tests. Later, nicotinic acid and fluoxymesterone (a vasodilator and a hormone preparation) methylphenidate and amitriptyline (a stimulant and an antidespressant) and thioridazine and meprobamate (a major and a minor tranquilizer) were administered for periods of up to 10 consecutive weeks and the effects evaluated in psychiatric, psychological and physical areas.

MH 08061
Herschel Liebowitz
Pennsylvania State University
University Park, Pennsylvania

Analytic Studies of Visual Perception

This investigator is conducting a research program into perceptual constancies. He is interested in individual and group differences and in relationships between the perceptual constancies and other

phenomena such as concept formation and stimulus generalization. An interesting finding is that shape constancy steadily declines from early childhood to adulthood. His studies have implications for the aged. They include studies of the role of experience in utilization of monocular cues in size perception, investigation of the relationship between the Ponzo illusion and size constancy, overage groups, analysis of cues underlying shape constancy by sequential presentation of object and ground, and studies of the effects of value on perceived size.

MH 08534
Robert Spitzer
N. Y. State Psychiatric Institute
Research Foundation for Mental Hygiene
Albany, New York

Evaluation of Psychiatric Status and History

This project is working towards providing the mental health professions with several highly structured and standardized interview procedures and rating scales. These standardized procedures may make it possible to assess the psychopathology of patients in different clinical settings in a uniform and objective manner and thus will greatly facilitate communication between workers in different installations. Among the instruments being developed is a Geriatric Form of a Psychiatric Status Schedule. The investigators are also developing computer diagnostic systems which will enable others to utilize the interview and rating scales of this project to classify patients into the diagnostic categories of the American Psychiatric Association's "Diagnostic and Statistical Mannual" with a high degree of interclinician reliability. It is expected that these instruments will prove valuable for research and improve communication between different research workers regarding the compositions of their samples of subjects, thus making for comparability of effort and outcomes.

MH 08556
Herman Buschke
Stanford University
Palo Alto, California

Retention in and Retrieval from Immediate Memory

The investigator is engaged in a series of experiments aimed at understanding immediate memory. Impairment of immediate memory functions characteristically occurs in the aged, mentally retarded, and brain damaged. A better understanding of the basic mechanisms of immediate memory may help in devising procedures for behavioral

rehabilitation of such patients. Experimental procedures for distinguishing between storage processes and retrieval processes have been developed, as have two types of experimental procedures for purposes of making independent estimates of the amounts in storage and the characteristics of the retrieval systems.

MH 10359
Stanley Samuels
New York University
New York, New York

Biomedical Studies of Senile Dementia

A three-year comprehensive biochemical study of dementing processes in man (Alzheimer's disease, senile dementia, cerebral arteriosclerosis) has been undertaken under this grant. The methodology is largely derived from biochemical programs on human neurological diseases developed in the laboratories of the late Dr. Saul Korey. The investigator has a dual approach to the problems: (1) attempts to isolate by gradient density procedures senile plaques, neurofibrils, and granular vacuoles from suitable animal and human autopsy materials, and (2) use of human cerebral biopsies from patients with dementias (together with suitable control specimens) processed for (a) structural chemical studies (nucleic acids, proteins, lipids, extractives), and (b) metabolic studies (oxygen uptake, substrate utliization, incorporation of labelled precursors, etc.). A possible relationship of cerebral zinc metabolism to senile dementia is emerging. Also, it is believed that the technique of rheography may aid in furnishing information about cerebral blood flow and its possible relevancy to senile dementia.

MH 10895
Paul McHugh
Cornell University Medical College
New York, New York

Visceral Function in Affect and Brain Disorder

This program on mechanisms of brain control of visceral responses is studying variations in plasma cortisol levels and gastric secretion in depressed, manic, and brain-injured patients. Adrenocortical studies in senile and brain-injured patients will also be done, using ACTH tests, dexamethasone and SU 4885. Senile and pre-senile patients will be selected from the neurological and psychiatric wards of Payne Whitney Clinic and Bloomingdale Hospital.

MH 10927
Irwin Feinberg
Research Foundation of State University
of New York
Albany, New York

Sleep Patterns in Mental Illness

A portion of this proposal deals with studying the sleep patterns of patients with chronic brain syndrome. The aim to determine whether sleep time is reduced or redistributed, and to gather further evidence on the apparent relationship of nocturnal delirim to awakening from REM (Rapid Eye Movements) sleep and of the degree of impairment to total sleep time. The investigator has interesting ideas concerning characteristic sleep patterns and the relationship of nocturnal delirium to stages of sleep at awakening.

MH 11668
George Engel
University of Rochester
Rochester, New York

Psychological Determinants of Organic Disease

This is a part of a larger investigation of the psychological concommitants of illness along a wide range of organic disease which is being carried out at the University of Rochester Medical School. Healthy aged persons, 90 years or older, and their families are heing interviewed regarding object relations, object relating capacity, self-image, incidence and character of separating experiences, incidence of giving up, helpless-hopelessness, incidence and nature of illnesses; and they are then being compared to other populations. Data is also being collected on the role of age in the projection of affects through drawings. Persons, ages 60 to 85, were asked to make drawings in response to the stimulus of an affect word. These drawings are being analyzed for color, theme, form and style in relation to each affect.

MH 12132
Chad Gordon
Age Center of New England, Inc.
Boston, Massachusetts

Personal Autonomy and the Social Processes of Aging

This project is an attempt to determine social and psychological conditions and processes by which the sense of personal autonomy is produced and maintained in relation to the problems and crisis of role alteration at forced retirement. One thousand persons employed

in companies following the policy of enforced retirement at age 65 will be given intensive one-hour interviews plus mail-back questionnaires to complete six months before retirement and at six and eighteen months after retirement. Major areas to be explored are: 1) adaptation, as described by knowledge and information, ability to get along with others, intelligence, energy and skills, 2) goal attainment, including independence, initiative, industry, and use of available opportunities, 3) integration, including unity of belief and value system, consistency of behavior and likes and dislikes as well as physical health, 4) pattern, including self respect and personal integrity, keeping physically fit and putting principles and beliefs into practice.

MH 12400
Aaron Antonovsky
Israel Institute of Applied Social
Research
Jerusalem, Israel

Socio-Cultural Patterns and the Involutional Crisis

The investigator is studying the differential effects that social roles have played and the values held by women in four ethnic groupings in Israel during pre-menopausal and menopausal periods of their lives. First a preliminary clinical study of the case records of 115 hospitalized cases and 50 social psychiatric open-ended interviews of two groups of European and Oriental patients is being undertaken. This is being followed by a study of four ethnic groups: European, North African, Persian, and Arab, each having two subgroups of 250 pre-menopausal (35-39 years old) and 250 menopausal (45-54 years old). Data is to be obtained by interviews scheduled with psychiatric, psychological, and sociological components. The focus is primarily on behavioral or attitudinal characterizations of the female social role and the anticipated or actual reaction to menopause. Medical records are available, if needed, and some physical examinations may be performed.

MH 12492
Barbara Anderson
California State College
Hayward, California

The Adaptive Task of Aging: A Psychosocial Analysis

This is a study concerning the "psychosocial theory of aging adjustment." This theory developed out of the conviction that guidelines for behavior in old age in American culture are poorly defined

and that the elderly face serious adaptational problems. The sample and the data to be used for this study were derived from 600 persons who were admitted to the psychiatric ward at the San Francisco General Hospital for the first time after they reached 60 years of age compared with 600 aged persons who were in the community. Forty aged persons from the overall community sample will be compared with 39 patients from the hospital sample.

MH 13434
Charles Eriksen
University of Illinois
Urbana, Illinois

Temporal Factors in Visual Perception Related to Aging

This research involves two pilot experiments to investigate certain temporal parameters of visual perception among different aged adults. The first experiment will study the critical duration time for form identification for subjects in the age range of 30-65 years. The critical duration time is a concept from Bloch's law and represents the temporal duration over which luminance and duration of a stimulus can be interchanged without affecting the performance criterion. The second experiment will investigate the temporal interval over which integration in pattern identification occurs in subjects in this age range. This latter experiment has relevance to the concept of a psychological moment and, to the extent that the concept is valid or useful, the experiment can be expected to provide information on the relation of aging to psychological time units.

MH 13682
Robert Herrmann
Boston University
Boston, Massachusetts

Tissue-Specific DNA-Histone Interaction

The immediate goal of this phase of the work is the study of tissue-and age-specific DNA-protein interaction in mammalian tissues. Should such specificity be demonstrable, investigators would next concern themselves with the physico-chemical aspects of the interaction and with the effect of the various histone fractions upon DNA-directed polypeptide synthesis in a cell-free system. The long range goal of this work is the understanding of the biochemical basis of development and aging.

MH 13821
Morton Kleban
Home for the Jewish Aged
Philadelphia, Pennsylvania

The Institutional Milieu of the Senile Patient

This pilot study of the institutional milieu of a ward for the mentally impaired aged patients will investigate personal and social behavior in the senile section of the hospital from an anthropological, participant-observation point of view. Variables relevant to the manner by which the resident lives and moves within his social and physical environment will be analyzed from object behavior recordings, with a view to manipulation of physical and social objects and determination of the effects on the patient's behavior. This pilot work will provide material for more formal research to be done in a building now being built especially for mentally impaired aged.

MH 14423
Charles Gaitz
Baylor University
Houston, Texas

Comprehensive Care of Suspected Mentally Ill Aged

This project was undertaken to demonstrate how comprehensive services can be provided by the community thus preventing unnecessary mental hospitalization of older inhabitants. The investigation was stimulated by a survey which indicated that many older persons were admitted to the State hospitals more for financial and social reasons than because of psychiatric disorders. One hundred consecutive applicants over age 65 are being studied by an interdisciplinary geriatric diagnostic team. Existing community resources plus services of members of the geriatric team are being utilized for rehabilitation and treatment. Before-and-after studies are being conducted on members of the experimental group, who are then being compared with a group of 100 individuals who had applied for admission before this program was initiated.

MH 14832
Bernard Stotsky
Northeastern University
Boston, Massachusetts

Study of Mental Patients in Nursing Homes

Though nursing homes have increasingly become important community

resources for the placement of aged State mental hospital patients, questions have been raised as to whether these homes are appropriate placements for this type of patient. It was out of these questions that this research developed. This study investigated the possible significant variables affecting the adjustment of State mental hospital patients to nursing homes. It examined the characteristics of nursing homes and the attitudes of their personnel which could have affected the adjustment of the former mental hospital patients. It attempted to predict the adjustment of a group of mental patients from a State mental hospital on the basis of these variables, the characteristics of the nursing homes and the attitudes of their personnel. It also carried out therapeutic intervention and evaluated the impact of such intervention on the patients' adjustment in the nursing home and on the attitudes of the nursing home personnel.

MH 14881
Daniel Wilner
University of California
Los Angeles, California

Psychosocial Factors in Housing for the Aged

This study is measuring the impact of different housing environments upon the mental and physical health of the aged. After a thorough housing survey, an experimental sample has been drawn from six housing facilities, representative of well-elderly at different levels of income, and matched with a control group of comparable individuals living in urban neighborhoods. A questionnaire, administered to 100 residents at each housing facility, is being administered to the control group with case-by-case matching. Among areas being investigated are the emotional and physical consequences of segregating older persons from younger age groups, of geographical remoteness from the extended family, and of high-density grouping of older persons. A social anthropological field investigation has been made at one housing facility to gain insight into a variety of sociological phenomena arising out of group residence.

MH 14888
Esther Twente
University of Kansas
Lawrence, Kansas

Mobilization of Aging Resources for Community Service

This project focuses on the mobilization of the population aged 65 and over for use in meeting current needs facing their rural community. It addresses itself to the concern about the lack of well defined social roles for the aging which would affect their mental health. It aims to: 1) Reduce the problems of the aging process through

the creation of a "community participant" role for the aging resident; and 2) Reduce community problems, in general through the utilization of aging persons.

The project was carried out in three parts: 1) a fact finding phase during which a community profile was constructed and the "Life Satisfaction" of the aging was determined; 2) a community development action program during which aging persons were mobilized into task forces and undertook various projects for the benefit of the community; and 3) an evaluation phase during which progress in the solution of community problems and changes in the "Life Satisfaction" of participating aging residents were evaluated.

MH 14889
Robert Kastenbaum
Mental Health Research Corporation
Boston, Massachusetts

A Training Program for Work with the Aged and Dying

This project focuses on the behavior and experiences of geriatric patients with special reference to dying and death. An attempt is being made to acquire descriptive knowledge about the terminal phase of life, develop and test specific hypotheses, and apply the obtained information to improving the care of geriatric patients. A psychological autopsy series is one of the focal points of this project--weekly multidisciplinary sessions organized around the case of a recently deceased patient for both research and training purposes. The project also includes a longitudinal panel of patients who are being studied to improve understanding of relative significance of ethnic background, personality and medical status upon the terminal phase of life. The project distributes an informative newsletter, OMEGA, to scientists and others concerned with problems of dying, death, bereavement and time perspective.

MH 14893
Gertrude Hall
National Council for the Aging
New York, New York

Guardianship and Protective Services for Older People

The plan of this project is to point the way toward development of an integrated approach to services and care of the mentally impaired aging, and to initiate improved methods for locating and helping these impaired older persons. Evaluation is now in progress of

one year's experience in demonstration service centers which were developed in Houston, San Diego, Philadelphia and Chicago. The different experiences in these cities are being compared and guidelines to facilitate the development of future services are being formulated.

MH 14894
Wilma Donahue
University of Michigan
Ann Arbor, Michigan

Milieu Treatment of Older Mental Patients

This is a grant for a 54-month research-demonstration study of milieu treatment with older patients in a mental hospital. It includes a 24-month study of four alternative treatment programs, using 200 male and 200 female patients, and a concurrent followup investigation of 120 patients who are discharged for further care to one of three types of community facilities. Its major aims are to determine the technology of milieu therapy for recently admitted and chronic mental patients, and to evaluate the effects of various milieu treatments, institutional-oriented versus community-oriented, on the post-hospital adjustment of patients requiring aftercare in nursing homes, foster homes, or group residential facilities. The project will also provide opportunities to develop training programs for scientists, professional and sub-professional persons preparing for work with the mentally-ill aged.

MH 14902
Walter C. McKain, Jr.
University of Connecticut
Storrs, Connecticut

Older Persons in Connecticut

This project has sought to identify factors related to the adjustment of widows and widowers who remarried late in life. The specific objectives of this research were the determination of the effects of their late remarriage on the mental health and stability of the aged couple and the development of greater understanding of the factors which encourage or hinder the adjustment of such couples. Information was obtained on their economic and health status and their social adjustment as influenced by their remarriage, as well as the attitudes of their children and the community and the impact of these attitudes on the couple's adjustment.

MH 14915
Jeanne Thune
Senior Citizens, Inc.
Nashville, Tennessee

A Study of Racial Attitude Changes in Older Adults

The aims of this study are 1) to determine whether racial desegregation changes occurring in the larger community are reflected in the behavior and feeling of the older negro and white population, and 2) to determine whether participation in a biracial social situation will bring about greater positive change in behavior and feeling than is occurring in the population at large. This study is being carried out through assessing attitudes and personality variables of older white and negro participants in an integrated Senior Citizen Center and comparing them with a control group of older whites and negroes active in other groups. Three hundred and twenty in four replication groups are tested at 6 month intervals.

MH 14917
Jean Carey
Community Service Society
New York, New York

Senior Advisory Service for Public Housing Tennants

The goal of this 4-year demonstration project is to demonstrate the manner in which an older non-professional worker can provide information and referral services to sustain emotional, social, and physical functions of elderly persons in public housing. The workers reach out to aged residents to make personal, neighborhood and community health and welfare services available to them when necessary. Four service workers are located, one each, in four housing projects, each containing some 300-500 who are age 60 or more. A fifth project is used as a control. Before and after interviews will be conducted on a stratified random sample of 100 older persons from each of the four housing projects served by the demonstration and 200 older persons drawn from the control project to determine the effectiveness of this service. Detailed analysis of data and description of procedures will be carried out.

MH 14923
Powell Lawton
Philadelphia Geriatric Center
Philadelphia, Pennsylvania

Social and Medical Services in Housing for the Aged

This is a study of the effects of various kinds of

services offered in group housing arrangements for aged individuals. Eight group housing settings, including public housing, nonprofit and commercial housing, are being studied as well as control groups of community residents. Sites offering one or more services in addition to housing will be compared with others not offering these services in terms of significant net changes in tenants' social adjustment and mental and physical health. Medical examinations, psychological tests and interviews will be the main sources of data. Intensive study of the process of socialization and community formation will be made in a limited number of sites. The characteristics of those who choose group living situations will be compared with those who remain in the larger community.

MH 14924
Clark Blackburn
Family Service Association of America
New York, New York

Social Work Team with Aging Family Service Clients

The overall goal of this study is to sustain the social, physical and emotional functioning of the aging client to enable him to live more effectively in the community through the enhancement of service with a social work team. Five member agencies of the Family Service Association of America were selected to carry out the aims of the project. These agencies are in Baltimore, Chicago, Cincinnati, Cleveland and Philadelphia. Teams consisting of a trained caseworker and a social work assistant, who is agency trained, carry cases. Where appropriate the continued support of the aged client is assigned to the assistant. In view of the short supply of trained personnel, determination of the areas in which the nonprofessional worker may appropriately function is expected to contribute to planning services for the aged.

MH 14926
Barry Nathanson
Hebrew Home for the Aged
Riverdale, New York

Workshop for Mentally Impaired Institutionalized Aged

This four-year demonstration program has established a sheltered workshop program for severely impaired brain syndrome patients in a home for the aged. Residents with four different levels of impairment are provided with the workshop experience plus a battery of supporting services. Medical, psychiatric and psychological tests and

case conference evaluations are being used to determine if such patients have the capacity to sustain participation in a work program and to derive therapeutic benefit from it as measured by maintenance of functional health situations and better adjustment to the infirmary environment. The program has been offered to 50 patients during the first project year, and from 75 to 100 during each subsequent project year.

MH 15020
Maurice B. Hamovitch
University of Southern California
Los Angeles, California

Housing Needs and Satisfactions of the Elderly

This study aims to investigate the specific types of housing arrangements which the aged perceive as ideal. A sample of 1700 elderly persons, now residing in various types of housing, age-segregated, non-age-segregated, urban and suburban, will be compared as to socioeconomic variables. Objective measures will attempt to identify the functions which elderly people would like housing to perform, the housing arrangements which would best meet manifest needs, the nature of satisfaction and dissatisfaction with various types of housing, and the patterns of relationship of need, need fulfillment and satisfactions, with personal characteristics and specified types of housing arrangements.

MH 15047
Elaine Brody
Home for the Jewish Aged
Philadelphia, Pennsylvania

Individualized Treatment on Mentally Impaired Aged

This project aims to demonstrate that mentally impaired aged patients are more disabled functionally than is warranted by the brain damage and have excess disabilities which are attributable to a variety of other physical, psychological and social factors. The investigator feels that a positive change in the individual's level of functioning can be achieved through systematic identification of factors and by means of an integrated program of diagnosis, treatment, re-evaluation, and reformulation of treatment goals. The experimental group of 32 patients is to be compared with a similar group of 32 patients receiving the traditional services and treatment at the same institution. Instruments are being used to measure modification of behavior, motor performance, self-care, social participation, cognitive functioning, and physical status.

APPENDIX C

LONGITUDINAL STUDIES

GOVERNMENT SUPPORTED LONGITUDINAL STUDIES

1. Longitudinal Program of the Gerontology Research Center, NICHD, NIH
   Baltimore City Hospitals
   Baltimore, Maryland
   Director: Nathan Shock

2. Study of Physiologic and Psychologic Aging in Pilots
   Lovelace Foundation of Medical Research and Education
   Albuquerque, New Mexico
   Director: Robert Proper

3. Normative Aging Study
   Veterans Administration
   Boston, Massachusetts
   Director: Benjamin Bell

4. Longitudinal Study of Aging
   Duke University
   Durham, North Carolina
   Director: Ewald Busse

5. Human Aging Project
   Philadelphia Geriatric Center
   Philadelphia, Pennsylvania
   Director: Samuel Granick

6. Brown University Longitudinal Study of Aging
   Brown University
   Providence, Rhode Island
   Director: Robert Burnight

7. Institute of Human Development Studies
   University of California
   Berkeley, California
   Director: Dorothy Eichorn

8. Intellectural Functioning in Later Life
   Age Center of New England
   Boston, Massachusetts
   Director: Paul Rhudick

9. Consistency of Personality and Adjustment in Old Age and the Problem of Survivorship
   Pennsylvania State University
   University Park, Pennsylvania
   Director: Joseph Britton

10. Pensacola Study of Naval Aviators
    Naval Aerospace Medical Institute
    Pensacola, Florida
    Director: Ashton Graybiel

11. The Atomic Bomb Casualty Commission Study
    Hiroshima, Japan
    Director: George Darling

12. The Tecumseh Community Health Study
    University of Michigan
    Ann Arbor, Michigan
    Director: Frederick H. Epstein

13. Studies in Geriatric Mental Illness
    Langley Porter Neuropsychiatric Institute
    San Francisco, California
    Director: Alexander Simon

14. The USAF Aerospace Medical Fitness Program
    USAF School of Aerospace Medicine
    Brooks Air Force Base, Texas
    Director: Timothy N. Caris

15. FAA Air Traffic Controller Health Program
    Federal Aviation Administration
    Washington, District of Columbia
    Director: Peter V. Siegel

Longitudinal Program of the Gerontology Research Center NICHD, NIH

This longitudinal Program is conducted by the Gerontology Research Center, the intramural research branch of NICHD. The Gerontology Research Center is located in a federal building on the grounds of the Baltimore City Hospitals in Baltimore, Maryland. The study was started in 1958. The Director is Nathan Shock, Ph.D.; Medical Director, Reubin Andres, M.D.; Program Statistician, Samuel Greenhouse, Ph.D.; Program Coordinator, Mr. Arthur Norris.

GOALS

The Central Goals of the Study are:

1) To create a data file which includes all the medical, physiological, biochemical, psychological, social, and other characteristics of the participants,

2) To compare the characteristics of participants of various ages,

3) To relate longevity of participants to individual characteristics and to factors which may be derived from two or more characteristics, and

4) To identify patterns of change of characteristics of participants with respect to direction and rate of change.

The investigators hope to compare the actual patterns of change with patterns that can be predicted from selected theories of aging in order to test the applicability of the various theories to the population being studied. This effort will necessarily be limited to those theories which involve characteristics that can be measured in living men. While it may not be possible to elucidate the cellular phenomena of aging in a human population, measurement of lifespan and its interrelationships with the maintenance of function of the organ systems should permit differentiation between two major classes of theories of aging, for example. Some theories assume that a few cells are lost during each unit of time so that changes of a gradual nature would be found. These theories are consistent with the summation of series of distributed minor accidents (such as radiation hits). Other theories would relate large changes in function with the occurrence of a disease episode, major accident, or unidentifiable event which results in a substantial loss of cells. These theories are consistant with abrupt changes in functional levels which would be maintained until another major alteration resulted in a new level. In addition, these two widely different types of theories could be found in combination (sudden as well as slow changes operating simultaneously).

SUBJECTS

The subjects of the study are volunteers recruited by existing subjects. The group can be characterized as highly educated (86 percent are college graduates), happily married, successful men who are employed in professional and administrative occupations. Retired members of the group continue to pursue activities which enhance their self-esteem and permit them to feel that they are making a useful contribution to society. At present there are about 630 participants who have been tested one time, 450 two times, 340 three times, 200 four times, 150 five times, 50 six times, 20 seven times, and 10 eight times. The distribution of participants by decade of birth is:

Decade of Birth	Age	Number
1860-69	98-107	2
1870-79	88-97	5
1880-89	78-87	52
1890-99	68-77	108
1900-09	58-67	124
1910-19	48-57	164
1920-29	38-47	128
1930-39	28-37	40
1940-49	18-27	7

VISIT INTERVALS

The visit interval is 18 months for participants below age 70 and is 12 months for those 70 and older. The tests performed on each visit are not identical, but the tests of the fifth visit repeat those of the first, the tests of the sixth repeat those of the second, etc. The test cycle is thus 6 years for the younger participants and 4 years for the older. The testing period is 2½ days each visit.

STUDIES PERFORMED

The tests which are included in the program fall into the following categories:

1) Pulmonary Function
2) Body Composition
3) Renal Function
4) Exercise and Neuromuscular Function
5) Psychological
6) Biochemical
7) Genetic
8) Nutritional

9) Sociological
10) Carbohydrate Metabolism
11) Hearing and Vision
12) Medical (Clinical)

The specific tests in each category are given in the appendix.

DATA STORAGE

All test results are recorded on cards which are maintained in an appropriate file. A systems analysis is being carried out to design an appropriate magnetic tape oriented data storage and retrieval system. The system will include editing systems for input, and updating systems and extracting systems for removing stored data from the system for statistical analysis.

DATA ANALYSIS

The standard methods of statistical analysis are available. Techniques for factor analysis, for dealing with unequal precision of measurements when changing from one laboratory method to another, and for sequential analysis involving a single variable are also available. Techniques for dealing with questions which involve changes and interactions of changes among several variables at several points in time are neither obvious nor available.

TESTS AND PROCEDURES IN THE BALTIMORE LONGITUDINAL STUDY

Lists of Tests	Performed on Visit No. 1	2	3	4
A. Pulmonary Function				
1. Vital capacity	1	2	3	4
2. Maximum breathing capacity	1	2	3	4
3. Maximum expiratory flow indices	1	2	3	4
4. Residual volume (N_2 washout)	1	2	3	4
5. Pulmonary gas distribution indices (N_2 washout)	1	2	3	4
6. Diffusing capacity (breath holding)				4
7. Pulmonary compliance				4
B. Body Composition				
1. Basal metabolism	1	2	3	4
2. 24-hour creatinine excretion	1	2	3	4
3. Anthropometric measurements	1	2	3	4
a. Behnke index		2		4

List of Tests	Performed on Visit No.			
	1	2	3	4
4. Body water	1			
a. Total body water	1			
b. Extracellular water	1			
5. X-ray bone density	1			
6. Skinfold thickness	1	2	3	4
7. X-ray fat thickness	1			
C. Renal Function				
1. Creatinine clearance test	1	2	3	4
D. Exercise and Neuromuscular Function				
1. Tapping test	1	2	3	4
2. Exercise screening battery		2	3	
a. Strength tests		2	3	
(1) Grip strength		2	3	
(2) Arm strength		2	3	
b. Low-level crank turning		2	3	
c. Maximal work rate (brief)		2	3	
3. Sub-maximal exercise with metabolic, ventilatory and cardiovascular measurements		2	3	
4. Activity history	1	2	3	4
5. Reaction time (touch)		2	3	
6. Reflex time		2	3	
7. Nerve conduction velocity		2	3	
E. Psychological				
1. Serial and paired associate learning tests	1			
2. Southern California tests of intellectual abilities	1			
a. Word fluency	1			
b. Associational fluency I	1			
c. Ideational fluency I	1			
d. Expressional fluency	1			
e. Consequences	1			
3. Semantic differential test	1			
4. Guilford-Zimmerman temperament survey	1			
5. Army alpha test	1			
6. Wechsler adult intelligence scale	1			
a. Vocabulary	1			
7. Benton visual retention test	1			

List of Tests	Performed on Visit No. 1	2	3	4
8. Problem solving (logical)			3	
9. Problem solving (concept)				4
10. Simple and choice reaction time measurements with physiological recording (electroencephalogram, galvanic skin response)		2		
F. Biochemical				
1. Total serum protein	1			
a. Serum albumin	1			
b. Serum globulin	1			
2. Serum cholesterol	1	2	3	4
3. Serum glycerides	1	2	3	4
4. Blood creatinine level	1	2	3	4
5. Nonprotein nitrogen	1			
G. Genetic				
1. Family history		2		
2. Smoking history	1	2	3	4
3. Taste test		2		4
4. Blood typing			3	
H. Nutritional				
1. Nutrition history		2		
2. Diet records		2		
I. Sociological				
1. Burgess-Cavan-Havighurst attitude questionnaire	1			
2. Questionnaire on attitude toward old people	1			
3. Personal interview			3	
J. Carbohydrate Metabolism Tests				
1. Fasting plasma glucose	1	2	3	4
2. Intravenous glucose tolerance test	1			
3. Oral glucose tolerance test		2		
4. Cortisone glucose tolerance test			3	
5. Tolbutamide tolerance test				4

List of Tests	Performed on Visit No. 1	2	3	4
K. Hearing and Vision				
1. Tonography	1	2	3	4
2. Vision test	1		3	
3. Color vision test	1		3	
4. Pure tone audiometry	1		3	
L. Medical Summary				
1. History	1	2	3	4
2. Physical examination	1	2	3	4
3. Neuromuscular evaluation	1	2	3	4
4. Chest x-ray	1	2	3	4
5. Electrocardiogram	1	2	3	4
6. Step-test electrocardiogram (Double Master)	1	2	3	4
7. Urinalysis	1	2	3	4
8. Hemogram	1	2	3	4
a. Hematocrit	1	2	3	4
b. White blood cell & differential count	1	2	3	4
c. Hemoglobin and M.C.H.C.	1	2	3	4
d. Platelets	1	2	3	4
9. Serological test for syphilis (VDRL)	1			
10. Cornell medical index health questionnaire	1			

Medical Chart Format:

1. White front sheet containing lists of diagnoses and code numbers.
2. White admission slip and observation notes.
3. History form (Longitudinal Studies).
4. Physical examination form (Longitudinal Studies).
5. Blue recommendations form (Longitudinal Studies).
6. Admission notes and order.
7. Progress notes (1 sheet).
8. Clinical laboratory report slips.
9. Pathology report, consultations (ordinarily not present).
10. X-ray report form.
11. Pulmonary report form (Longitudinal Studies).
12. Basal Metabolism report form (Longitudinal Studies).
13. Medical laboratory report form (Longitudinal Studies).
14. EKG report form.
15. EKG record.
16. Temperature record.
17. Correspondence to and from family physician (except routine correspondence).

Study of Physiologic and Psychologic Aging in Pilots
Lovelace Foundation for Medical Research and Education

The Lovelace "Study of Physiologic and Psychologic Aging in Pilots" is carried out at the Lovelace Foundation for Medical Research and Education in Albuquerque, N.M., and is supported by research grant HD 00518 from NICHD. It was started about 1960. Robert Proper, M.D. is the Principal Investigator; Ulrich Luft, M.D. and Jacek Szafran, Ph.D. are Co-Principal Investigators. Francis Wall, Ph.D. is in charge of statistical evaluation.

GOALS

The goal of the study is the measurement of changes in physiological and psychological function in professional aviators, an unusually physiologically and psychologically endowed group of persons.

It is hoped that appropriate compilations of data will be valuable in the determination of physiological age. The possibility of predicting longevity and vascular accidents is hoped for. Comparisons of the rate of aging in different organ systems are well under way.

SUBJECTS

One hundred subjects are being collected from each decade from the 3rd through the 7th for a total population of 500 male subjects. Two thirds of the test subjects are airline pilots, flying primarily jet transport aircraft, ¼ are military jet pilots, and the remainder are test pilots, flying X-15 and similar aircraft. Most of the pilots enter the study as a result of personal referral by other subjects in the group.

VISIT INTERVALS

Subjects are re-tested at five-year intervals in order to check upon the reproducibility of the testing procedures and the normal variation to be expected in testing results. Tests are completed in one day.

STUDIES PERFORMED

The tests which are included in the program fall into the following categories:

1) Anthropometric
2) Cardiovascular
3) Pulmonary

4) Psychological
5) Special Senses
6) Medical
7) Exercise Tolerance

The specific tests performed are described in the appendix.

DATA STORAGE

Samples of hard copy, photographic, analogue and digital data are kept in individual envelopes for each subject. A folder containing the digital data, as reduced from analogue signals is kept in a separate file. The digital data are also stored on magnetic tape. A copy of the magnetic tape is stored separately.

DATA ANALYSIS

All data are used in the determination of simple means and standard deviations. All data have been subjected to statistical correlations. Segments of the data have been subjected to partial correlations. Much of the data are presently being subjected to step-wise regression, and non-linear relationships are being scrutinized. Comparisons of the rate of aging in different organ systems are well under way. Computer analysis is undertaken on the Burroughs 5500 digital computer. This medium size computer has two disc modules, magnetic drums, and a core memory of 16,000 words. Data recorded in the laboratory as analogue signals on magnetic tape are currently being run through an analogue to digital converter. It is hoped that electronic analogue to digital conversion will facilitate data reduction but experience in this area is still preliminary.

PILOT TESTING SCHEDULE

7:00 to 7:15 A.M.
24 Hour Urine Collection Started for Creatinine Clearance
Weight (Kg.)
Electrocardiogram (Lead 1)
Finger Plethysmography (Lacey)
Electrical Impedance Plethysmography (Nyboer, right and left calves)
Skin Temperature (Centigrade)
Blood Pressure (right and left arms)

7:15 to 7:30 A.M.
Electrocardiogram (Frontal, Lead 1)
Pulse Wave Velocity
Precordial Acceleration Tracing
Phonocardiogram
Altec Vibrocardiogram

Ballistocardiogram
  Displacement, Velocity and Acceleration
  HME with EKG
  HME without EKG
  HMI
  HFI
  HFE

7:30 to 7:35 A.M.
Ride Monark Bicycle Ergometer (5 minutes with 2 Kg. load)
  Altec Vibrocardiogram
  Phonocardiogram
  Precordial Acceleration Tracing
  Carotid Pulse Tracing
  Electrocardiogram

7:35 to 8:00 A.M.
Electrocardiogram (Lead 1)
Precordial Acceleration Tracing
Ballistocardiogram
  Displacement, Velocity and Acceleration
  HME with EKG
  HME without EKG
  HMI without EKG
Pulse Wave Velocities
Phonocardiogram
Altec Vibrocardiogram
Finger Plethysmograph
Electrical Impedance Plethysmograph (Right and left calves)
Skin Temperature
Blood Pressure (Right and left arms)

8:00 to 8:15 A.M.
Electrocardiogram (Einthoven and Precordial)
Vectorcardiogram (Frank)

8:15 to 8:30 A.M.
Dry and Submerged Weighing for Body Volume and Density

8:30 to 9:15 A.M.
Pulmonary Function Studies
  Total lung capacity and all subdivisions by direct and indirect spirometry
  Intrapulmonary mixing from nitrogen dilution record
  Flow volume loop of forced inspiratory and expiratory vital capacity
  Pulmonary diffusing capacity (Steady state CO_2 method)

9:15 to 9:30 A.M.
Coffee and Doughnuts

9:30 to 10:30 A.M.

Physical Competence Test
- Electrocardiogram
- Blood Pressure and Pulse (Taken every minute)
- Oxygen Intake
- CO_2 Output (According to body weight in kilograms)
- Respiratory Exchange Ratio
- Inspired Volume
- Expired Volume

10:30 to 11:30 A.M.

I^{131} Study of Cardiac Output
Carotid Blood Flow (Qualitative)
Popliteal Blood Flow (Qualitative)
Renograms
Cerebral Blood Flow (Qualitative)
Blood Volume
Serum Creatinine (Drawn at this time)

11:30 to 11:45 A.M.

Anthropometric Measurements
- Height (Standing and sitting)
- Upper Arm Circumference (Right and left arms)
- Chest Diameter (Lateral, anterior to posterior and biacromial)
- Chest Circumference (Normal, full inspiration, full expiration)
- Skin Fold (Right and left upper arm and right and left subscapular)
- Manuometer Strength (Right and left hand)
- Radial Measurement (Right and left hand)
- Vibrations (Right and left malleolus)
- Dominant Hand

11:45 to 12:00 Noon

Physical Examination
Apexcardiogram
Altec Vibrocardiogram
Phonocardiogram
Electrocardiogram (Lead 2)
Statham Accelerometer

12:00 Noon to 1:00 P.M.

Lunch

1:00 to 3:30 P.M.

Sensory Perception Studies
- Bekesy Audiometry (Threshold fluctuations in quiet and in noise; sweep and fixed frequency tracings)

Tachistoscopic Recognition Thresholds (Under baseline, 'visual noise' and divided attention conditions)
The Course of Dark Adaptation (Goldmann-Weekers) and Photostress Test (Return visits, time permitting)
Critical Flicker Fusion Frequency and Minimum Perceptible Inter-Signal Interval
Visual Accommodation

3:30 to 5:00 P.M.
Study of High-Speed Sequential Decisions
Serial Choice Reaction Times (Baseline rate of gain of information)
Serial Choice Reaction Times under Conditions of Information Overload (Estimate of reserve channel capacity; with short-term memory sub-task; and with verbal sub-task and under conditions of delayed auditory monitoring of speech)
Psychological Refractory Phase (Return visits, time permitting)
Information Transfer Functions in Compensatory Tracking (Return visits, time permitting)

5:00 to 5:30 P.M.
Assessment of Intellectual Status and Appraisal of Personality
Progressive Matrices (Raven)
AH 5 (Time permitting)
WAIS - Abbreviated Procedure (Time permitting)
Maudsley Personality Inventory
Personal Information (Handedness and laterality preferences, flying experience, etc.)

Normative Aging Study
Veterans Administration

The Normative Aging Study is carried out at the VA Outpatient Clinic, Boston, Massachusetts, and is carried out as a direct research operation of the Veterans Administration. Historically, the longitudinal plan was preceded by a multidisciplinary investigation of Spanish-American War veterans. This preliminary phase of the Normative Aging Study took place between 1958 and 1963 in a specially created geriatric facility of the Boston Outpatient Clinic. Benjamin Bell, M.D., is the Director of the study, and Charles Rose is the Assistant Director. Many investigators collaborate in this study. This includes investigators from the Retina Foundation, an ophthalmological research center, the Department of Dermatology at Harvard Medical School, the Department of Psychiatry at the Massachusetts General Hospital, etc.

GOALS

Each subject will be followed periodically over the course of his lifetime to learn what changes occur at what time and under what circumstances. The major aims of the study are to describe the changes that occur over time, to make validated predictions, and to make correlations among the large number of variables studied. The longitudinal design will delineate true age changes, which is not accomplished by cross-sectional analysis, where different age groups are compared at a given point in time. Cross-sectional studies may be misleading because they depend on inferences as to what might happen under certain conditions and assumptions, whereas longitudinal studies determine what actually does happen as well as when and how it happens. An illustration would be changes in stature arrived at cross-sectionally which are not borne out by longitudinal analysis. In cross-sectional analysis, the changes indicate shrinking in stature during adult life. This has not been found in longitudinal studies. The amount of shrinkage in cross-sectional studies can be accounted for by known secular changes (stature of population is increasing over time) or by selective survival (short people live longer).

A special feature of the sampling design will make it possible to parcel out the effect of secular change from the effect of age difference. The sample is composed of a series of cohorts: a group who entered the study at age 25-29, a group who entered at age 30-34, a group who entered at age 35-39, and so on. Thus, different subjects will reach a given age at different times. For example, a 50-54 age group entering the study during the period 1965-1969 (Group I) may be compared to a group who entered the study during the same period at age 30-34 and attain age 50-54

twenty years later (Group II). In other words, at the period 1985-1989, Group II will be the same age as Group I was at the period 1965-1969 and the difference between the two along with data from other groupings and longitudinal analysis could afford insight into the effect of secular change.

The Normative Aging Study is a broad interdisciplinary investigation which includes medical and dental evaluation, body build and function, biochemistry, perception, and behavior. The focus of interest is on the mutual interrelationships of these parameters and their changes with age, rather than on development of disease. Many subjects, of course, will develop some illness, despite the application of rigid health criteria in their selection. The more common illnesses such as hypertension, coronary heart disease, and periodontal disease should occur often enough to warrant statistical analysis for predictive or correlation purposes. Such correlations would include levels of blood pressure, serum lipids, and electrocardiographic changes with the development of heart diseases; and levels of serum pepsinogen with the development of peptic ulcer. Prediction of disease may in fact turn out to be an important dividend of this longitudinal health study.

SUBJECTS

A total of 2000 male veterans rigidly screened for an initial high level of health are under study. These subjects ranged in age from 25 to 75 years at the time of entry into the study and included all ethnic, socio-economic, and occupational groups in the Boston population.

The screening of subjects is an elaborate, expensive procedure because of the strict criteria involved. The screening battery was designed to do double duty by providing baseline data for comparison with subsequent examinations. It was found, however, that subjects were rejected overwhelmingly for reasons that could be quickly and inexpensively determined, such as blood pressure, pulmonary function, blood sugar and problems detectable by chest x-ray and electrocardiogram. Accordingly, a prescreening procedure was devised which, by rejecting applicants prior to expensive laboratory screening, reduced the subsequent rejection rate from 50 percent to 10 percent.

At the present time, the screening process can be summed up as follows: 1) To begin with, our publicity stresses the rigid health requirements of the study. Presumably, this results in some self-screening. 2) As part of their application, candidates fill out a medical questionnaire designed to eliminate persons with

known disqualifying disease, present or past, such as cardiovascular disease, mental disorder, peptic ulcer, and the like. This step eliminates 10 percent of the applicants. 3) After passing this hurdle, the applicants are called in for prescreening. Fifty percent of the remaining candidates are rejected at this stage. 4) The final stage consists of a thorough medical examination, plus a detailed biochemical and physiological test battery. Values exceeding normal laboratory limits are repeated and if they remain abnormal, subjects are rejected. Ten percent of the survivors of prescreening are rejected at the final stage. Thus, of ten applicants to begin with, four are finally accepted into the study. It is interesting to note that at prescreening the rejection rate is 50 percent, despite the fact that in our publicity and recruitment procedures we state that only individuals in excellent health and with no history of major disease or injury should apply, in view of our objective to study "healthy aging." Nevertheless, many apply to become subjects because they have some anxiety about their health and feel that volunteering to be subjects could be a painless way of finding out. Also, many people are simply not aware of their blood sugar or blood pressure.

The decision to study initially healthy individuals and to rigorously screen prospective subjects for this purpose has produced a problem, namely a screening procedure which is relatively more rigorous on older subjects entering the study. This is because the same screening criteria were applied regardless of age. As a result, cross-sectional analysis may be prejudiced, since age differences between older and younger subjects have been reduced. For this reason, it is planned to study the "rejects" (of which the study has as many as acceptances) in order to make comparisons between them and the accepted cases. To this end, careful records of the rejected cases have been kept. These can be brought into the study at a later date when the budgetary base of the study can be expanded. The inclusion of less than healthy groups will also have the salutary effect of broadening the base of medical interest in the study. Specifically, the comparison of initially rejected and initially accepted cases may uncover different patterns of age changes.

VISIT INTERVALS

Currently the subjects come in for 3 half days over a 5-year cycle. However, this can be expanded to 10 half days over a 5-year cycle.

STUDIES PERFORMED

The studies performed fall into the following categories: general and miscellaneous, sensory, dental, anthropometric, and biochemical-physiological.

Under general and miscellaneous are included medical examination, chest x-ray, electrocardiogram, pulmonary function tests, perception, information processing, personality function tests, intellectual function tests, strong vocational interest tests, and sociological tests.

The auditory functions tests include auditory responses to pure tones and speech discrimination as well as time-altered speech stimuli. The visual studies include these areas: acuity, tonometry, dark adaptation, dynamic, static and flicker perimetry, sensitivity to scotomic glare, turbidity of the ocular media, depth perception, and detailed drawings of the fundus by indirect binocular ophthalmoscopy and scleral depression. Smell and taste are being studied in connection with the dental studies using as a criterion of measurement the rate of parotid secretion to appropriate stimuli.

The emphasis of the dental research is on facial bone measurements. This area was selected because of the complete absence of data beyond age 20 and its relevance to the engineering problem of dental prothesis.

The morphological investigations are very detailed. The anthromorphological data will be related to illness, longevity, and cause of death.

Biological and physiological observations include standard blood and urine examinations, liver function tests, serum pepsinogen, triglycerides, protein electrophoresis, and thyroid parameters. Serum testosterone analysis is in the planning stage. Salivary steroid levels are being explored as indices of stress, aging and disease.

DATA STORAGE

The data are placed on tape at the computer of the Smithsonian Astrophysical Laboratory in Cambridge, Massachusetts, and computations can be carried out through a data link with one of its peripheral processors.

DATA ANALYSIS

A group of statistical consultants has been appointed to develop multivariate procedures for the longitudinal study.

Longitudinal Study of Aging
Duke University

The Duke "Longitudinal Study of Aging" is carried out at the School of Medicine, Duke University in Durham, North Carolina, and is supported by research Grant HD-00668 from NICHD. It was started in 1955. Dr. Ewald Busse is the Principal Investigator. Core project investigators have included internists, opthalmologists, psychiatrists, neurologists, psychologists, sociologists, and social workers.

GOALS

The Duke Study of Aging was initiated to investigate the processes of aging among a panel of non-institutionalized males and females 60 years of age and over from the time of initial observation to death. The study was conceived as exploratory and multidisciplinary. The organization was intended to facilitate the accumulation of the widest possible range of observations from investigators with a variety of theoretical perspectives on a common panel of subjects. Medical, psychiatric, psychological, and sociological perspectives have been represented among project investigators over the first decade of the project's existence.

No single theory of aging informed the development of the study. The focus has been on the generation of hypotheses as much as the testing of hypotheses of interest to a variety of investigators who have brought quite different theoretical perspectives to bear on the analysis of data. The project, therefore, has offered each investigator an opportunity for contact with colleagues with different theoretical interests and perspectives and an opportunity for the use of the data of other investigators as control variables in his own research on panel members. Senior investigators on the project have also developed satellite studies to test specific hypotheses generated by findings based on panel data.

SUBJECTS

The centrality of detailed information on medical and psychological functioning which required precise measurements and laboratory evaluation presented a special problem in the development of a panel of older subjects. Two days of examination in a medical center setting were required. The reported experience of survey research indicated that refusal to participate by subjects was a function of age in the later years. Since the proposed examination of panelists was costly and continued participation in the panel was vital, the Duke investigators chose to recruit volunteers rather than attempt to involve a randomly drawn sample of non-institutionalized subjects.

A technique was used in which recruited volunteers were used to recruit additional volunteers. The subjects were 60 years of age or older. Initially the median age of panelists was 70, and they ranged in age from 60 to 94. From this pool a panel was created that reflected the age, sex, ethnic and socio-economic characteristics of the older population in the locale. The purpose of this procedure was to maximize the variety of controls which might be introduced subsequently, not to give the appearance of random sampling without its substance (Maddox, "A Longitudinal Multidisciplinary Study of Human Aging: Selected Methodological Issues," Proceedings of the 1962 American Statistical Association, 280-285).

VISIT INTERVALS

Two days of study in a medical center setting are required for each examination. Four examinations have been made of the panel of subjects. The dates of the examination were 1955-59, 1959-61, 1964-65, 1966-67.

STUDIES PERFORMED

The tests performed fall into the following categories:

	Items of information
Medical	336
Psychiatric/Neurological	109
Psychological	109
Social	234

In somewhat more detail they may be listed as follows:

Medical History
Physical Examination
Neurological Examination
Mental Status
Mental Status (Special)
Depression and Hypochondriasis
Dermatological Examination
Ophthalmological Examination
  Visual Fields
  Acuity
  Color
  Depth Perception
Special Vision Tests
Audiometry
  Pure Tone
  Speech Threshold

Electroencephalogram
Chest X-ray
Laboratory Studies
  Urinalysis
  Blood Morphology
  Blood Chemistry
  Serologic Test for Syphilis
  Cholesterol
  Urea Nitrogen
Medical Summary
Psychological Data
Learning and Memory
Special Psychological Data
Reaction Times
Social History and Information
Retirement Data

Medical determinations included history and current status of systems with special attention being given to cardiovascular ratings, serology, opthalmology, and audiology. A summary rating of physical functioning was developed for estimating the presence or absence of pathology and associated degrees of disability. An index estimating cardiovascular functioning has been developed.

The psychiatric/neurological variables focus on aspects of mental status and functioning, both current and historical, among panelists. Detailed EEG evaluations supplement the findings of neurological examination.

Psychological variables include WAIS scores, assessment of reaction time in a variety of learning experiments, and summaries of Rorschach responses.

Sociological variables include life style indicators: work status and history; family relationships; and level of activity and of life satisfaction, including an adaptation of Cavan Activities and Attitudes scales.

DATA STORAGE

Observations on subjects are recorded on precoded schedules from which, in the typical case, data are punched directly on cards for transfer to computer tape. When the schedule calls for a summary indication of complex phenomena, space is provided for investigators to give detailed functional descriptions of the data which underlie their summary so that reliability estimates can be made.

Complete protocols, including laboratory reports, are retained for each subject in addition to data decks and a continuously updated computer tape. This tape is stored at the Triangle Universities Computing Center for use of IBM 360/75 hardware. Although IBM 360/30 hardware is available at the Computing Laboratory on the campus and 360/1050 low speed terminals are available in the Department of Sociology and in the Medical Center, most computations are carried out on the 360/75.

Inquiries about the use of project data by investigators not associated with the project are welcomed. Since complete code books are available and complete data stored on computer tape, an interested investigator could, in collaboration with a senior investigator associated with the project, request specific runs of the data to be made.

DATA ANALYSIS

The relevant software for the 360/75 is FORTRAN, PL/1, and TSAR. TSAR (Tape Storage and Retrieval) is a package of subroutines developed initially for the Longitudinal Study of Aging at Duke. Originally programmed for IBM 7072 hardware, TSAR permitted an investigator to ask for a specific statistical routine to be performed simply by specifying transformation and grouping indicators along with the procedure name. For example, one could call for means and standard deviations by calling simply for MEAN; or for a 3-way analysis of variance with the specification ANOVA 3-way. Similarly, covariance correlations, regression, plotting, and certain non-parametric procedures could be called for with minimum instructions. With the advent of new hardware, not all of the procedures have been adapted but a substantial part of the TSAR program has been retained as a subroutine. Discriminant function subroutine is currently available and a subroutine for the Detection of Interaction Effects, adapted from the work of Sonquist and Morgan at the University of Michigan, is currently being perfected. Walter Obrist has experimented with analog to digital conversion in his EEG analysis.

Human Aging Study
Philadelphia Geriatric Center

BACKGROUND

An interdisciplinary team from the National Institute of Mental Health carried through an extensive and intensive biological and behavioral study of a group of healthy aged men during the period of 1955 to 1957. In 1962 the surviving subjects were recalled to the Clinical Center of the National Institute of Mental Health where a somewhat abbreviated form of the original study was administered. During 1967 and 1968 the surviving subjects were once again located and this time re-examined (also to a somewhat abbreviated extent) at the Philadelphia Geriatric Center. The original study involved an analysis of over 600 biological, psychiatric, social and psychological characteristics of the subjects. The procedures and the analysis were reported in book form, edited by James E. Birren, Robert N. Butler, Samuel W. Greenhouse, Louis Sokoloff and Marian R. Yarrow, entitled Human Aging, A Biological and Behavioral Study (PHS Publication - No. 986, U.S. Government Printing Office). The five year follow-up of 1962 has not been as yet fully analyzed, but several brief reports have been published in medical, psychological and psychiatric journals. The 12 year follow-up has recently been completed and the data have been analyzed to a considerable extent. Reports in the medical, psychiatric, social psychological and psychological areas are being prepared.

GOALS

1. The central goal of the original or initial study was to focus on the normal aging process and to delineate those changes which could be attributed to the phenomenon of growing old from the changes brought on or significantly influenced by disease factors.

2. In addition to describing the aging process of the various aspects of the human organism, the investigators intended to clarify their inter-dependencies.

3. The two studies which followed pursued the same goals and oriented themselves further toward developing a description of the natural course of development or aging through the late or concluding portion of the life cycle.

4. The intention was also to develop a comparative analysis of survival versus mortality and thus to seek possible biological, psychosocial and behavioral factors which might be related to extended longevity.

5. A basis was, furthermore, sought for describing the adaptations to social and personal change in individuals as they move through the eighth and ninth decades of life and to learn about such personal reactions as their self concept, views of the environment, body image, and time, and how they use their energies.

SUBJECTS

A group of 47 men over the age of 65 was selected from a somewhat larger group of volunteers from the Philadelphia, Pa., and Washington, D.C. areas. Each subject was selected on the basis of advanced age, apparent good health and independent community living. Careful and extensive medical study led to splitting of the subjects into two sub-groups, one group of 27 which was free of any significant physical symptoms and a second group of 20, each of whom presented some subclinical or asymptomatic features. The mean age of all the subjects was 71.5 (range being 65 to 92). Religious distribution was 20 Jewish, 23 Protestant and 4 Catholic. Educational background was of a wide range for the group, 20 being grade school or less, 11 having some or completed high school and 11 having some or completed college. Economic level of three fourths of the group was comfortable, the remainder were able to manage adequately. Thirty-two of the men were married, fourteen were widowed, or separated and one had never married. Generally, therefore, the group was atypical on social-personal characteristics for their age grouping, just as they were above average for medical status.

By 1962, at the time of the first follow-up, 39 of the subjects had survived and it proved possible to interview and examine 38 of them. For the second follow-up in 1967-68, there were 23 survivors. The average age of this group at the time of the original study had been 70 years, and for the deceased subjects, 72.9 years. Of the remaining 23 subjects it proved possible to interview and examine 19.

DATA STORAGE

The scores and tabulations of the data are on file at the Biometry Branch of the National Institutes of Mental Health. The book, "Human Aging", referred to above, also contains tabulations of original data collected on the 47 subjects.

DATA ANALYSES

Standard techniques of statistical analysis have been used, deriving means, standard deviations, t-Tests, Chi Square and F-Tests. Correlation analyses have also been used. In addition, factor analyses have been carried through to isolate specific factors associated with the aging process.

STUDIES PERFORMED

The following table lists the examination and tests and notes which were administered at each of the examination periods.

EXAMINATION TEST	PERIOD OF STUDY 1956	1962	1968
Biological			
Hematology	X	X	X
Blood Chemistry	X	X	X
Blood Pressure	X	X	X
Vascular System Study	X	X	X
Pulmonary Functions	X	X	X
Chest X-Ray	X	X	X
Skull X-Ray	X	X	X
EKG	X	X	X
Cerebral Blood Flow Test	X	X	X
EEG	X	X	X
Medical History	X	X	X
Urinalysis	X	X	X
Neurological Survey	X	X	X
Physical Examination	X	X	X
Height	X	X	X
Weight	X	X	X
Auditory and Vestibular System History	X		
Otoscopic Examination	X		

EXAMINATION TEST	PERIOD OF STUDY 1956	1962	1968
Audiometric Examination	X		X
Click Perception Test	X		
Delayed Speech Feedback Test	X		
Psychological			
Wechsler Adult Intelligence Test	X	X	X
Raven Progressive Matrices	X	X	X
Wisconsin Card Sorting	X	X	
Speed of Card Sorting	X		
Learning	X		
Addition Rate	X	X	X
Arithmetic Alternations Rate	X	X	X
Speed of Copying Digits	X	X	X
Word Fluency	X		
Perception of Line Difference	X	X	
Reaction Time	X	X	
Mirror Tracing	X		
Stroop Test	X		
Level of Aspiration Test	X	X	
Draw-a-Person	X	X	X
Weigl Color Sorting	X		
Emotional Projection Test	X		
Thematic Appreciation Test	X		
Family Scene Test	X		X

EXAMINATION TEST	PERIOD OF STUDY 1956	1962	1968
Homonym Test	X	X	
Sentence Completion Test	X		X
Rorschach	X	X	
Minnesota Multiphasic Personality Inventory	X		
Social Psychological (Interviews)			
Family History	X		
Educational History	X		
Occupational History	X		
Retirement Planning	X	X	X
Marital History	X	X	X
Living Arrangements	X	X	X
Use of Time	X	X	X
Social Relations and Interaction	X	X	X
Attitudes Toward Life	X	X	X
Goals and Aspirations	X	X	X
Critical Turning Points in Life	X	X	X
Significant Losses	X	X	X
Observed Physical and Mental Changes in Aging	X	X	X
Psychiatric (Interviews)			
History of Psychiatric Contact	X		
Personal Social History	X		
Psychiatric Sympton Check List	X	X	X

EXAMINATION TEST	PERIOD OF STUDY 1956	1962	1968
Mental Status Evaluation	X	X	X
Concept Evaluation:			
Futurity	X	X	X
Death	X	X	X
Self Concept	X	X	X

Brown University Longitudinal Study of Aging
Brown University

This panel study is the main undertaking of the Center for Aging Research established at the University by the National Institute of Child Health and Human Development under PHS Grant HD 00671. The Center is part of the Department of Sociology and Anthropology, although it is located in the Institute for Health Sciences building with which it also has close affiliation.

The study is a collaborative effort by three quite varied sociologists and a medical researcher who formerly was a leading Providence physician. Perhaps its most distinctive feature is the close collaboration developed, cutting across biological and social science lines. The senior research staff includes: Martin U. Martel, Associate Professor of Sociology, specialist in sociological theory, methodology and sociology of aging; Robert G. Burnight, Professor of Sociology, demographer and methodologist concerned with epidemiological aspects of adult aging; Alex M. Burgess, Jr., M.D. in the Departments of Preventive Medicine at Harvard and Medical Sociology at Brown University; Eugene A. Friedmann, Professor of Sociology, social gerontologist with special interest in changing work, family and medical-utilization patterns affecting older adults.

GOALS

Broadly, the aim is to study longitudinally the effects of health decline and illnesses on social roles, role capacities, and life satisfaction--by men and women entering the post-adult period. More specifically, the study seeks information about age-related changes in:

1) Overall health and vitality

2) Specific illnesses

3) Health care and medical utilization

4) Income, financial needs and financial dependency

5) Social activities (primarily work and family, but also including friendships, organizations and leisure)

6) Changing abilities to perform valued activities

7) Adjustments to illness, retirement, income-loss, widowhood, and other crises characteristic of the particular age group.

Emphasis is placed upon the variable linkages between (a) organic changes discernible to respondents and their physicians, and (b) activity patterns relating to important roles and relationships. Our main linkage concept for relating organic changes to social participation is the notion of role-capacities: that is, the abilities of individuals to perform activities essential to their livelihood, autonomy and their way of life. In contrast with the more general notion of "impairment", this conception explicitly focusses on how biological changes and specific illnesses affect the activities that are important for individuals in various walks of life.

In addition to its substantive aims, the study also attempts to contribute in several ways to the more effective longitudinal analysis of longitudinal-survey data. Recent advances in available computer resources open the doorway to far more effective analyses. Considerable efforts have been made to develop improved methods for:

1) Recoding change-indicators for 3 panel rounds

2) Validation of scales based on interview responses

3) Validation of illness reports, more specifically, through a questionnaire survey of interviewee's physicians

4) Computer screening of complex change-relationships between large numbers of variables, and clear presentation of results for interpretations.

SUBJECTS

1) A Panel was formed in 1961 using area probability methods, consisting of 605 married couples (non-institutionalized and white), with husbands between ages 60 and 64, residing in Providence, R.I. The aim was to find a sample:

a) Socially and culturally diverse

b) Still actively participating in adult roles, but at an age where major health and activity changes soon could be expected for many (which could be followed up within a few-year period, to study health variations and their consequences).

c) Unrestricted by particular institutional affiliations.

2) Couples were taken as sampling units so that spouse influences on illness and treatment (as well as subsequent effects)

could be investigated. In restricting the age of sampled husbands but not wives, it was assumed that married women in our society typically first encountered problems of health decline through those experienced by their husbands.

In order to locate as diverse and unbiased a sample of eligible couples as possible, a canvas of 16,000 randomly selected households was made in 1961. This turned up a potential sample of 670 couples with whom first interviews were obtained with 605 (or about 90%). By the third and final interview--conducted from 40-48 months after the first--nearly 100 panelists had died, and several hundred were lost due to critical illness, moving or defections. Three complete interviews were obtained with 721 "loyalists", or about two-thirds of surviving panelists. (A detailed multivariate analysis of panel losses has been made.)

RESEARCH SCHEDULE AND INTERVIEWING

Broadly, the work of the study divides into four main parts:

1) Year #01 (1961-62): Staffing, panel design and selection.

2) Years #02-#05 (1962-66): Three panel-interviews--data collection and processing with some analysis of the first two rounds.

3) Years #06-#07 (1966-68): Preparations for 3-round analysis.

4) Year #08 (1968-69): Beginning of 3-round panel analysis.

Three sets of interviews were sought with husbands and wives in three quite detailed and structured interviews:

1) Interviewing Schedule

1st Interviews	Summer 1962
2nd Interviews	Summer 1963
3rd Interviews	Fall 1965-Spring 1966

2) Separate interviews were conducted with husbands and wives whenever possible. (An aim realized with most wives, and about 80% of the husbands)

3) A special interviewing staff of about 20 women was recruited and trained for each survey round. Because of the increased technical demands of the 3rd round:

a) The interviewing staff was restricted to graduate nurses or social workers.

b) Bi-lingual interviewers were sent to foreign born panelists (especially Italians and Portugese).

4) Interview coding for each survey round was done with unusual care and thoroughness (a task again requiring a staff of 20, mostly former interviewers, working for about a year to process each set of interviews).

5) Some follow-up interviews "in depth" were obtained shortly after the 3rd interviews, with panelists reporting new health difficulties in several categories. Some additional follow-ups of this kind are planned before the analysis is through.

DATA COVERAGE AND SOURCES

In the first interviews, panelists were questioned about their family backgrounds, birthplaces, residences and earlier careers. Following this, a core set of questions were raised that were repeated in the two succeeding rounds. These dealt with:

1) Overall health and vitality (self-ratings, comparison with others and with past)

2) Specific illnesses and injuries (modification of National Health Survey approach with additions)

3) Health care, expectations, and related attitudes

4) Medical utilization (doctor visits, treatments, hospitalizations)

5) Medical expenditures (costs, sources of help, resources)

6) Finances (income, other expenditures, satisfaction, needs)

7) Physical impairments

8) Role activities, satisfactions and expectations concerning:

a) Work
b) Family (most detailed)
c) Friendships
d) Neighborhood activities
e) Organizations
f) Church
g) Leisure pursuits

9) Specific role-capacities, difficulties, changes

10) Time - orientations

11) Religious beliefs and practices

12) Housing arrangements

13) Age-attitudes

14) Overall satisfaction (also goals, interests, worries)

The largest sections of the interviews were devoted to detailed inventories of role activities, difficulties and health problems. Since each time the questioning went back over the year or two preceding, the span of information gathered is roughly five years. In addition, the third interviews were expanded in their time coverage to include questions about activity changes since middle age, as well as a lifetime review of health difficulties and illnesses.

In addition to the interview information:

1) Record checks have been made through a variety of sources to check on interview reports where comparisons are possible and also to follow mortalities.

2) Doctor survey: After the third interview, questionnaires were sent to closest physicians of the panelists as a check on current and chronic illness reports. This survey was conducted between November 1966 and March 1967; and analysis work presently is near completion.

DATA STORAGE

The completed schedules for all three interview rounds (our basic data source for most characteristics) are systematically filed by couples in the Institute for Health Sciences where they are readily accessible.

1) IBM Card File. After each interview round, both structured and open-ended responses were coded and keypunched on cards to make computer processing possible. All basic data in this form are stored in Brown University's Computer Center (some 130 recording decks).

2) A Master Work Tape then was created that now contains more than 1,000 indicator-codes for each 3-round panelist as well as available information on all other interviewees. Most codes on this tape are recodes developed for special analysis purposes. All data are filed by respondent number and can be expanded, re-coded and updated by our Data Preparation programs.

3) Special tapes also have been created for specific analysis purposes, or for exceptional data problems like those raised by the Physician Validation Survey (where data are filed in part by physicians and by illnesses).

4) A transfer to a #2316 Disk Pack of all individual and couple data is expected in the near future for greater access speed. No programming changes are required.

DATA ANALYSIS

The development of more effective analysis methods for multivariate panel analysis (mainly of qualitative data) has been one aim of the study, as noted above. Much effort during the last three years has been devoted to this aim.

Our analysis approach represents an elaboration of Paul Lazarsfeld's "rotational" approach to multivariate "specification" of qualitative data.

The new models and strategies developed permit a far more comprehensive multivariate analysis of change-linkages: where variables are many and case numbers, relatively, are few. The general approach adopted (still under experimental advisement) is as follows: (1) The analysis is divided into phases, each centering on a dependent-variable area; (2) Each phase is broached by examining successively the associations of large numbers of variables with the dependent variable, seeking to eliminate those which show little predictive strength; (3) Surviving predictive-variables then are tested for independence under successive 3rd variable controls; (4) A decomposition of Fisher's Exact Test--decomposed for each cell in a multivariate table--is used as a significance test both in screening 1st-order associations as well as multivariate controls; and (5) Change-relations are compared with single-round associations in a modification of the Lazarsfeld-Campbell "cross-lagged correlation" idea.

The approach greatly increases the comprehensiveness of one's data-search, compared with standard survey analysis procedures in use; and helps to guard against the perenial problem of "spurious" survey findings. While the basic approach developed can be used to advantage in a single-round (non-longitudinal) survey, it has particular advantages in panel surveys because of the far greater statistical burden placed on sample size.

Institute of Human Development Studies (Berkeley Growth Study, Guidance Study, and Oakland Growth Study) University of California at Berkeley

The Berkeley Growth Study, the Guidance Study, and the Oakland Growth Study are continuing longitudinal studies by the Institute of Human Development, University of California at Berkeley. The major support for these studies over the approximately forty years of their existence has been University funds and grants from private agencies. However, each of these studies has within the last decade had substantial support from the National Institute of Mental Health either for data collection or data analysis or both. An intergenerational study combining the three generations of parents, subjects and children of all three studies has been approved for funding by NICHD.

The principal investigator for that project is Dorothy H. Eichorn, Ph.D., and the co-principal investigators are Marjorie P. Honzik, Ph.D., and Henry S. Maas, Ph.D. Past and current investigators include psychologists, sociologists, physicians of several specialities, geneticists, and physiologists. The Institute encourages use of its archives and facilities by qualified students, faculty, and staff, as well as by investigators from other institutions, subject to restrictions to maintain subjects' privacy and preservation of original records.

GOALS

The Berkeley Growth Study began as an intensive investigation of physical, mental, and motor development, but some assessment of personality characteristics of mother and child were included for their bearing upon the primary variables. As the study continued into adulthood, the original objectives were retained, but increasing attention was given to obtaining additional data on other behaviors, attitudes, interests, and familial background so that interrelationships of certain aspects of personality and environment could be examined. The Guidance Study was originally designed to determine a) how frequently the personality and behavior problems seen in therapeutic clinics occurred in a normal cross-sectional sample, b) some of the bio-environmental factors associated with the presence or absence of such problems, and c) whether the children's behavior was influenced by intensive discussions with parents about training procedures, personality characteristics of family members, interpersonal relationships, health, background, and social status. As the subjects moved into later childhood and on toward adulthood, the original objectives were transposed into a long-term study of personality development and its bio-environmental correlates. The

Oakland Growth Study had as its original aims the examination of physical, physiological, and personal-social (particularly peer group interaction) development during adolescence. Adult assessments emphasized social relationships within familial, employment, and community settings; satisfactions, dissatisfactions, competences, and liabilities in these settings; social mobility; personality characteristics; and physical and emotional health.

Although these three studies varied in original primary emphases, they have in common not only certain classes of data, but also three general research objectives, namely, the assessment of interpersonal continuities and discontinuities, their personal and environmental correlates, and patterns of interaction among central variables. Periodic data collection in the adult years has been maintained because a subject pool whose life histories have been so well documented offers an increasingly valuable and unique resource for pursuing these major developmental problems across the lifespan. Further, extended study of these subjects, their parents, spouses, and children makes it possible to address such important issues as the heritability among human beings of physique, physiological functions, intellective abilities, and personality traits and the extent and mode of cross-generational transmission of life styles and patterns of familial organization.

SAMPLE

In the Berkeley Growth Study efforts were made to obtain a small, homogeneous sample of healthy, hospital-born infants for frequent and intensive study. Babies born in the county hospitals and one private hospital were sought to broaden socio-economic representation. The study pediatrician obtained permission from delivering obstetricians to visit their patients and request participation in the study. Of the 75 mothers thus contacted, the 61 who provided the initial sample were white, English-speaking, and largely native born, Protestant, and of middle or higher socio-economic status. The original 61 infants were born within the period September 15, 1928 and May 15, 1929. During the following three years some families left Berkeley, and replacements were recruited. During 1964-1966, when the 36-year data were collected, 54 subjects were assessed, and some data were obtained on an additional seven subjects. Thus, of the 63 subjects who had been followed through at least the first three years, 61 were seen during their mid-thirties.

The Guidance Study sample was drawn from a survey that included every third child born in Berkeley during the period between January 1, 1928 and June 30, 1929. Direct data collection began when the children were 21 months of age, and at this time the 248 children

were divided equally between an experimental (Guidance) group and a control group that received objective measurements but no parental guidance. At the time of the thirty-year follow-up, the 169 subjects remaining (69% of the 21-month sample) were very similar to the original sample in socio-economic background.

The Oakland Growth Study sample consisted of slightly over 200 children from the high fifth and low sixth grades of five elementary schools in Oakland who planned to attend the junior and senior public high schools selected as the center for research observations. The subjects seen in the 1958 and 1964 follow-ups (about 2/3 of the original sample) did not differ significantly from the original group nor from the sample remaining at the end of high school in socio-economic status and a number of other personal or social characteristics.

VISITS

The subjects of the Berkeley Growth Study were seen by the study pediatrician during the first four days of life. Visits were then scheduled every month for the first fifteen months, every three months from 18 through 36 months, semi-annually from 3½ through 18 years, and at approximately 21, 26 and 36 years. Intensive data collection in the Guidance Study began at 21 months, but a public health nurse visited each home every three months from three- to 21 months, and circumnatal data were also obtained from physicians and hospitals. Subjects and their mothers were seen at 21 months and every six months from age two to four years, then annually to 17 years. About two-thirds of the subjects' spouses and about 300 of their children were also assessed when the subjects were seen at approximately age thirty. Subjects in the Oakland Growth Study were assessed semi-annually between approximately 11 and 17 years of age at the Institute and were observed and tested at other times in school and social situations. Several follow-ups, which reached some 60 to 80 of the most accessible subjects, were conducted when the subjects were in their early thirties. A more intensive effort, reaching over 100 subjects, was carried out in 1957-60. Some data on 27-45 additional subjects when in their thirties are also available. A survey of current occupational status, familial relationships, and drinking and smoking practices was carried out by interview and mail questionnaire in 1964, reaching 129 subjects for at least part of the data collection. As part of the projected intergenerational study, the subjects of the Guidance and Oakland Growth Studies would be seen at approximately age 40 and 50 respectively, and their parents at ages ranging from approximately 60 to 90.

STUDIES PERFORMED

In the Berkeley Growth Study standardized individual tests of intelligence and an extensive battery of anthropometrics were

collected at all ages. In addition, reflexes, pulse rate, respiratory rate, and blood pressure were taken during infancy. Body build photographs were taken at 21 months and annually from 3 through 18 years. Health records were made at all ages, and medical examinations were done annually from two through 12 and at 36 years. Gross motor tests were administered through nine years, strength tests from eight to eighteen and at the adult visits, and manual skills tests from 4½ to 9 years and periodically through 15 years. Thirty subjects received the physiological battery of the Oakland Growth Study at about 10 years. Behavior ratings and notes were made at all ages, and projective tests, leisure-time, interest, and personality inventories were administered on an irregular schedule. At 36 years intensive interviews were conducted. Mothers were observed and rated during the first two years, and ratings of mother and home were made when the subjects were preadolescent. Spouses have been tested and measured as adults, and children have been followed longitudinally. Some demographic data and observations are available on both generations.

In the Guidance Study concentration at all ages was on personality as measured through interviews with parents, teachers, subjects and spouses; ratings by interviewers, testers, and examiners; sociometrics; questionnaires; and projective tests. Standardized mental tests were obtained at 21 months, semi-annually through four years, annually through ten years, and at 12, 14, and 18. Medical examinations, including heart rate and blood pressure, and health records, height, weight, and body build photographs were taken at 21 months and annually from 3 through 18 years. From 8 to 18 a limited number of anthropometric and strength measures were also taken. All types of measures except the x-rays were repeated at thirty years.

For the Oakland Growth Study sample data secured for all subjects included rating by adults of behavior in a variety of social situations; sociometrics; self-reports on a wide variety of inventories of adjustment, interests and attitudes; teachers' ratings; mother's reports on habits and regimes; medical examinations; health histories; visual tests; strength tests; anthropometrics; x-rays; body build photographs; and intelligence and achievement tests. One half of the sample also received various physiological measurements, including assessment of cardiac, respiratory, and metabolic function, urine analysis, and Galvanic Skin Response.

In all three studies at least minor data collections, for example, on occupational, weight, residential and smoking history, have been made by mail within recent years.

DATA STORAGE AND ANALYSIS

For each subject there is a folder of original materials with an individual summary tabulation; some individual materials are filed by category rather than by individual. For most types of data, master tabulations have been made of original scores and of summary scores for each measure. In appropriate instances individual growth charts or individual tables across time have been constructed and filed as a group. All major panels of data are on cards and/or magnetic tape. As new data are collected, they are prepared for the computer and transferred to cards and/or tape. Master cross files and indices of original data, tabulations, cards, and data analyses are maintained for each study, as are publication lists. For each study there are also master charts of the instruments used at each age.

In addition to descriptive statistics, standard scores, factor scores and summary scores are widely used. For many behavior-personality assessments, scales had to be devised, and the original data transposed to them. Inferential scales, pooling a number of behaviors and data on behavior from a number of sources, have also been developed. Dimensions of behavior, physique, etc., are often established by factor analysis, cluster analysis, Q-sort or canonical correlation. Since the early 1950's a succession of computers have been available, but these have, of course, required constant re-programming.

Intellectual Functioning in Later Life
Age Center of New England, Inc.

The research project "Intellectual Functioning in Later Life" is being conducted at the Age Center of New England, Inc., located at 115 Newbury Street, Boston, Mass. The Age Center, incorporated in 1955 and conducting gerontological research continuously since that time, is an independent non-profit research organization. Its financial structure depends on grants from the National Institutes of Health (at the present time two projects: "Intellectual Functioning in Later Life" and "Personal Autonomy and Retirement"- MH-HD 12132), gifts from companies, and gifts from individuals. The project "Intellectual Functioning in Later Life" funded by NICHD as grant HD 01735 began on April 1, 1966 and is scheduled to end on March 31, 1971. The principal investigator is Paul J. Rhudick, Ph.D. The Director of the Age Center is Natalie H. Cabot.

GOALS

The primary goals are:

(1) to add 700 complete Wechsler Adult Intelligence tests, hereafter "WAIS", on males and females between 50-90 years of age to the normative data already being collected at other gerontological centers. The reason for collecting more normative data is critical because several authors, including this principal investigator, have found the proposed Kansas City standardization norms for the WAIS instrument inadequate, primarily in the area of overweighting the influence of chronological age. Collecting additional WAIS's would add to the expanding studies using the WAIS and allow for more generalization of findings and improve upon reliability and validity. This may be of great importance because one of the findings that is clearly emerging is that healthy aging persons beyond retirement age still maintain a high level of intellectual efficiency which could be utilized by society.

(2) to compare cross-sectional vs longitudinal approaches to the study of aging and IQ. To date, the literature is replete with pros and cons in respect to both approaches but no study yet has systematically compared both approaches <u>simultaneously</u>.

(3) to study the factor structure of intelligence in the light of age differences over time. The WAIS lends itself to factor analytic procedures and the underlying structure of intellect of different ages can be detected and compared. It should be added that the factor structure will be examined in the light of sex, health, retirement, socio-economic, and personality variables.

(4) to study the patterns of rise or decline in IQ in relating to initial intellectual endowment. Based on other data e.g. amount and type of education, prior IQ tests (in school systems) etc. estimates can be made of the initial level of IQ endowment which then can be compared with outcome in the later life.

(5) to study the complex interrelationship between health changes, aging, and IQ via questionnaires and actual physical examination.

(6) to study the effects of varying test-retest intervals on IQ scores. To date no study has systematically studied the "test-wiseness" that may develop as a function of the WAIS being administered more than one time. Most investigators have "intuitively" believed that a six-month to one year interval is necessary to mitigate against practice effects. However, it may be possible that "test-wiseness" may appear in only several of the subtests and not on all of them. This project will introduce an experimental variation in which a select number of subjects will be retested at intervals separated by only 24 hours, 48 hours, one month, two months, 3 months, 6 months, to determine specifically how much test-wiseness does develop and how much permanent vs impermanent knowledge is maintained.

(7) to study the effects of IQ changes on survivorship and time of death. This area is of great importance and recent literature currently, though scanty, tends to indicate higher survival in the higher IQ subjects. Also, some work by Jarvik et al indicates that drops in scores on certain subtests are portents of impending death. The N's are small and one focus of this project specifically is to collect more data so that these notions can be examined in depth.

SUBJECTS

The subjects, male and female, 50-90, retired and working, are community residing individuals located primarily in the Boston metropolitan area.

The subject pool comes from four sources:

(1) a self-selected pool of subjects who are volunteers and who have been members of the Age Center as "research partners" since 1955. Of this subsample, 120 males and females, average age 73, have been given the WAIS (beginning in 1960). Thirty of the original 120 have died. During the grant period all of these surviving subjects will be retested regularly at one year intervals.

(2) a sample of 200 subjects who participated in a recent three-year U.S. Public Health Service study (CH 23-6) conducted at the Age Center. These subjects were part of a pool of 1,780 persons selected from these representative wards in Boston by probability sampling (to correct for volunteer bias in the above described subsample). Of these 200 subjects some will receive the WAIS plus the other research instruments (see appendices) yearly, some every other year, and some at year 1 (1966) and years 4-5 (1970-1971). They will be used to test the effect of varying test-retest intervals and amount of change within intervals.

(3) a third sub-population of 200 subjects again previously selected for U.S. Public Health Service study CH 23-6 but who were used primarily as controls i.e. did not participate in the Age Center study via interviews and examinations, having received only a questionnaire through the mail. This group further controls for self-selected and volunteer biases, and possible psychotherapeutic influences from membership or exposure to the Age Center.

(4) a fourth population of about 100 subjects being brought in for two ongoing studies (Personal Autonomy--previously mentioned, and a Harvard School of Public Health study on Anthropometric measurement). Added to this pool are new members being recruited from church groups, business, etc. who wish to belong to the Center upon retirement.

The subjects are highly educated, motivated, successful, independent, and self-managing individuals. While the range includes blue and white collar workers occupationally, the bias is in the direction of white collar. They are psychiatrically and medically sound for the most part. Their IQ level on the average is superior (124).

VISIT INTERVALS

For the initially tested sample (beginning in 1960) the frequency of testing will be yearly. The reason is that this group will constitute a genuinely longitudinal sample i.e. an eleven year span (1960-71). For the various other subgroups described previously half in each will be tested yearly and the other half twice in the project span.

A select sample will be tested at very short interval ranges (24 hours, 48 hours, 1 month, 2 months, 6 months) on an experimental basis to test for practice effects.

BATTERY OF TESTS AND ASSESSMENT MEASURES

1) WAIS: all subjects

2) Minnesota Multiphasic Personality Inventory: in addition to the basic psychiatric scales, nearly 200 subscales will be used. Also 77 subscales devised by the Massachusetts Mental Health Center (based on valid clinical sensitivity) will be employed in the analysis.

3) Cornell Medical Index

4) Complete Physical Examination

5) Interpersonal Check List (Leary)

6) Current History (occupation, income, etc.): used to update information between test intervals.

7) Demographic data: ethnic group, socioeconomic level, etc.

STATISTICAL PROCEDURES AND DATA REDUCTION

A special system program called MASTER, written for the Age Center of New England for data storage and retrieval, is now in use at the Age Center. This program takes data from respondent's original data cards and stores them on a computer tape in such a fashion that at any point in time it is possible to add on new information for current respondents or even add on data from new respondents. The program enables the investigator to obtain summary information on the number of usable responses on each variable and the current status of each person's file. The system can also update information in terms of answers on each variable or in terms of number of questions answered.

The retrieval segment of the program allows the investigator to request any number of selected variables or any definable set of respondents, so that any analytic deck of selected variables can be constructed.

A special analytic program called PANEL has been written for the Age Center. This program performs any number of turnover (change) analyses. PANEL enables the investigator to cast the data in the form of turnover table, thus giving the response categories of Time 1, Time 2, Time 3, etc. in such a way as to permit assessment of stability and change. The program will present a statistical assessment of the change.

The full facilities of the Harvard Computational Center are available as well as the library of analytic programs.

Consistency of Personality and Adjustment in Old Age and the Problem of Survivorship
Pennsylvania State University

A research project, "Consistency of Personality and Adjustment in Old Age and the Problem of Survivorship," was started in 1955 at The Pennsylvania State University, University Park, Pennsylvania, with Joseph H. Britton, Ph.D., and Jean O. Britton, Ph.D., as principal investigators. A report of the longitudinal aspects of the study is in preparation and the project is scheduled for completion in 1969. The project has been supported by NICHD through Research Grant HD 01757, and by funds from the Pennsylvania Agricultural Experiment Station and from the University.

GOALS

The purpose of this investigation is to study some behavioral processes of aging, first by examining the consistency and change in personality and adjustment of older adults over time, and secondly, by determining the relationship between change in personality and adjustment and change in certain personal and environmental or situational factors. Further, since survival of persons is a selective process, survivors and non-survivors of the years of study are being compared in order to show some psychological correlates of survival.

In this study, aging is viewed developmentally, as change over time, in contrast to differences between age groups. Furthermore, aging persons were studied in their "natural habitats"--in their own homes in the community in which most of them have lived the major portions of their lives.

Personality and adjustment are defined in terms of both their "inner" or personal and "outer" or social aspects. The assessment procedures include standarized inventories, projective methods, ratings by judges, and evaluations by members of the community. To study the problem of survivorship, statistical comparisons are made between survivors and non-survivors using demographic and psychological data.

SUBJECTS

The subjects for this investigation constituted all of the residents of a rural community who were able and willing to be interviewed and given psychological tests three times over a nine-year period. The community consisted of a village and the surrounding township, comprising some 2,000 persons, and is located

in central Pennsylvania. A "census" of the study area was taken in 1955 by means of a house-to-house survey, when the social norms of the community were also investigated.

Two hundred and five persons aged 64 or over were listed in 1955; one year later, in 1956, 176 persons 65+ were still living and in the community. Of these individuals, 46 (17 men and 29 women) survived the nine-year period of the study and were interviewed and tested on all three occasions--in 1956, 1962, and 1965. The disposition of the original study population over the years is of special interest. Since there is little mobility in the area, particularly among these age groups, the non-participants are mostly those who have died or were too old and ill or refused to be interviewed. The last group has been relatively small.

An additional 73 persons (34 men and 39 women) who had turned 65 since the study began were entered as longitudinal subjects in 1962 and tested then and in 1965.

VISIT INTERVALS

The original older subjects were interviewed and tested on three different occasions--in 1956, 1962, and 1965. The subjects added to the study in 1962 were assessed then and in 1965, and they may again be seen late in 1968.

STUDIES PERFORMED

For this study, adjustment involved older persons' activities, their attitudes toward themselves and their activities, their attitudes toward other persons, and others' attitudes toward them. Several measures were used:

1) The Chicago Attitude Inventory (constructed by E. W. Burgess, Ruth S. Cavan, and R. J. Havighurst) has been used widely in studies of the aged; it measures satisfaction with the ordinary activities of life and general feelings of happiness and usefulness.

2) The Chicago Activity Inventory (devised by Burgess, Cavan, and Havighurst) uses objective questions concerning actual participation in various personal and social activities and concerning health problems.

3) The Judge's Adjustment Scale (devised by Cavan) obtains judgments of an individual's behavior (as revealed in interview material) in terms of his satisfaction with social relationships and his attitudes toward self.

4) The Personal Relations (P) Scale and the Sociability (S) Scale from the Guilford-Zimmerman Temperament Survey measure attitudes toward relations with other persons and general interest in and enjoyment of other persons. Certain of the P and S items were adapted for use.

5) Three cards (6BM, 7BM, and 10) from the Thematic Apperception Test were used to measure older adults' attitudes toward themselves. Each of the pictures included an older person; in the analysis of the stories, the main older person in the story was evaluated, for example, in terms of his adequacy in initiating action, his self-confidence, intellectual functioning, and inter-personal acceptance.

6) The Opinion Conformity Scale was based on the 1955 information on the community's expectations for older adults. It measured older persons' agreement with the predominant opinions of the community.

7) The Community Rating Scale provides an evaluation by selected residents of a sample of the subjects. The panelists used a Q-sort procedure to rate subjects on five aspects of their functioning in the community: respect, value of opinion, conformity, consideration for others, and friendships.

8) Interviewer's Ratings were based on direct observation of the subject's ability to interact, see, hear, and cooperate in the interview situation.

DATA STORAGE

Records, including interview and test forms, judges' ratings, scoring and coding procedures, have been maintained on the original groups of subjects and on the survivors who were followed over the years of the study. The records have been stored in locked files accessible only to persons working under the direct supervision of the investigators. Much of the data have been transferred to machine cards.

DATA ANALYSIS

The data have been analyzed in terms of frequency distributions, measures of central tendency and of variability at various points in time. Correlations have also been used to show inter-year change or consistency. A "longitudinal trend score" which would indicate the extent to which an individual tended to change over the years was devised especially for this study. The data were processed using Penn State's computational services.

Pensacola Study of Naval Aviators
Naval Aerospace Medical Institute

The Pensacola Study of Naval Aviators, commonly termed the "Thousand Aviator Study," began in July 1940 as a survey to validate techniques for preselecting pilot trainees in order to reduce the large attrition rate in the flight training program at that time. After World War II the investigation was continued with emphasis shifted to an evaluation of the cardiovascular system. The group, which now has approximately 792 survivors, in active military, retired, or civilian status, has been reexamined in 1951, 1957, and 1963. The Study Team, under the direction of Ashton Graybiel, M.D., at the Naval Aerospace Medical Institute, Pensacola, Florida has added new physiological measures with each successive evaluation. The new examination is scheduled to begin in 1969.

CURRENT GOALS

Medically Oriented

1. Obtain normative and baseline data on healthy young men.

2. Follow changes in baseline measurements as a function of age.

3. Correlate 1 and 2 with the appearance of cardiovascular abnormalities.

4. Define, retrospectively, precursors of cardiovascular disease.

5. Point out preventive and therapeutic measures.

Flight Oriented

1. Contribution toward delineation of the optimal cardiovascular assessment of the flyer in terms of

   a. Career
      1) Initial selection: Emphasis on physiological, metabolic, and psychological "indicators" of later appearance of disease and disorder.

      2) Periodic examination

         (a) Routine: Emphasis on diagnosis of underlying disease and short-range prediction of susceptibility to an acute cardiovascular incident.

(b) Comprehensive: Supplement to routine examination at critical ages of important stages of careers.

b. Mission (assessment in terms of professional responsibilities)
1) Stress tests

2) Prediction (likelihood) of an acute cardiovascular incident over the period of the mission

2. Implications for prevention of acute incidents or chronic disease.

3. Evaluation of effects of flight stress by comparison with nonflying professional groups.

SUBJECTS

From the original exploratory study of pilot selection evolved a longitudinal study with cardiovascular emphasis unique in several respects:

1) The mean age of its participants at inception of the program was 23.6 years, and all except thirteen were between 20 and 30 years of age.

2) The entire group was remarkably homogeneous. All were white males in the military serving as flight instructors or students. All were of similar health, size, education, and social background.

3) All candidates were physically fit, without visual or motor defects, of "normal" intelligence, and very competitive in spirit. It was perhaps these latter qualities which made them a highly motivated experimental group. One thousand and fifty-six (1056) men formed the nucleus for the 1951 and succeeding evaluations. Proper identification of the subjects and finding of up-to-date addresses for each member constituted a prodigious task.

EXAMINATION INTERVALS

At the time of the original study no thought was given to the possibility of a long range follow-up study but, after a lapse of ten years, it seemed clearly desirable to attempt it. Subsequent examinations were done at six-year intervals. The dates of the examinations were 1940, 1951, 1957 and 1963.

STUDIES PERFORMED

1940 Study The testing program was organized so that each cadet was assigned to the Research Laboratory for one full day as an official part of his indoctrination into the Naval Air Station. This assignment occurred during the first week of his tour before any flight training. Data were obtained from the following:

1. Personal and Medical History
2. Physical Examination
3. Cardiovascular Tests
    a. Schneider Index of Neurocirculatory Fitness
    b. Tilt-Table Response
    c. Cold Pressor Test
    d. Electrocardiography
4. Pulmonary Function and Metabolic Studies
    a. Breathing Pattern
    b. Tidal Volume
    c. Vital Capacity
    d. Basal Metabolic Rate
5. Anthropometry
    a. Somatotype
6. Psychological-Psychomotor
    a. Mental Ability
    b. Mechanical Aptitude
    c. Athletic Achievement
    d. Eye-Hand Coordination Test
    e. Two-Hand Coordination Test

f. Mashburn Serial Action Apparatus

g. Dotting Test (McDougall)

h. Continuous Reaction Test (Cattell)

i. Ataxiameter (Miles)

j. Tilt-Chair

7. Vision

a. Aniseikonia

b. Photographs of Eye Movements (Ophthalmograph)

c. Dark Adaptation (Wald)

8. Neurophysiological

a. Electroencephalography

b. Skin Resistance

1951 Study As the subjects were located, questionnaires were mailed to them requesting information concerning their recent activities and general health. The follow-up examinations were conducted by a team from the Naval School of Aviation Medicine traveling by plane or by converted carry-all truck to various locations in the United States. The mobile unit contained portable x-ray equipment, two electrocardiographs, and the requisite equipment for conducting a physical examination. Subjects were examined at their residence, place of business, in the truck, or wherever possible; subjects located overseas were examined by local medical facilities of the armed forces and the results forwarded to the School of Aviation Medicine. It was not possible to adhere to a formal schedule or test sequence either by the team or elsewhere because of obvious limitations, but all results were recorded on Navy Standard Form 68. Data were obtained from the following.

1. Interview - Personal and Medical History

2. Physical Examination

3. Cardiovascular Tests

a. Electrocardiography

4. Anthropometry

5. Teleoroentgenograms

1957 Study This examination was conducted in the same manner as the 1951 Study. A team traveled throughout the country to examine the subjects usually in available government medical facilities, but if necessary in their homes. Data were obtained from the following:

1. Interview - Personal and Medical History

2. Physical Examination

3. Cardiovascular Tests

   a. Cold Pressor Tests

   b. Electrocardiography

   c. Ballistocardiograms

4. Laboratory Determinations

   a. Blood Cholesterol

   b. Serum Lipoproteins

5. Anthropometry

6. Teleorentgenograms

1963 Study The 1963 evaluation was designed to be the most comprehensive survey of the participants to date. These men had now reached an age when detection of latent disease was an extremely important consideration. With the interest and support generated by the previous evaluations it was possible to perform thorough examinations at the Naval School of Aviation Medicine, in contrast to the previous follow-up examinations which by necessity were conducted by a team of Navy physicians who traveled about the country in a mobile laboratory unit. The ability to bring the subjects to Pensacola enabled the investigators to carry out the more desirable detailed physiological appraisal not possible in the previous two examinations. The men were provided commercial air transportation to Pensacola for two days of extensive testing in which every significant physiological measurement included in the earlier examinations was repeated. In addition, certain tests either not always possible in the field or not previously available were carried out.

Also due to increasing interest in the program at this time the Thousand Aviator Study gained the support and assistance of the Heart Disease Control Program of the U.S. Public Health Service in the form of financial aid, equipment, and personnel. Plans were formulated to continue this study indefinitely at intervals of three to five years.

Preliminary questionnaires were sent to 815 participants during the latter part of 1962, requesting information concerning their recent health, occupation, flying and military status. Actual testing began in January of 1963 and continued until the Spring of 1965. An attempt was made to standardize all procedures insofar as possible. Data were obtained from the following:

1. Interview - Personal and Medical History
2. Physical Examination
3. Cardiovascular Tests
    a. Electrocardiography
    b. Plethysmography
    c. Ballistocardiograms
    d. Vectorcardiograms
4. Laboratory determinations
    a. Hematocrit
    b. White Blood Cell Count
    c. Differential Cell Count
    d. Urine Albumin and Sugar
    e. Serum Cholesterol
    f. Serum Lipoproteins
    g. Protein-Bound Iodine
    h. Uric Acid
    i. Triglyceride Values
    j. Glucose values by method of Somogyi

5. Pulmonary function and metabolic studies

    a. Spirometry with a 13.5 L Collins Apparatus

    b. Pulmonary Curves by Med-Science Wedge Spirometer

6. Anthropometry

    a. Heights (standing and sitting)

    b. Weight

    c. Skinfolds

    d. Circumferences

    e. Diameters

    f. Hand Grip

    g. Somatotype

7. Teleoroentgenograms

8. Psychological - Psychomotor

    a. Guilford Zimmerman Temperament Survey

    b. Graybiel-Fregly Ataxia Test

    c. Tilt-Chair Test

9. Vision

    a. Tonometry

    b. Retinal Photographs

10. Neurophysiological

    a. Electroencephalograms

11. Audiometry

    a. High Frequency Audiogram

    b. Naval Aviators Speech Discrimination Test

DATA PROCESSING

Compilation of data has taken many different forms. Special indices were computed from various formats tuned to the computer facilities available at the time of analysis. In the 1940, 1951, and 1957 studies, the data for each individual subject were grouped, analyzed, and placed on punch cards for convenience and as a permanent record. The data processing equipment available during the 1963 evaluation consisted of an IBM 1620 computer and accessories. Most programmed statistical procedures involved the common measures of range, means, standard deviations, skewness, and correlation coefficients. The formula of R.J. Wherry (in Stead, W.H. and C.P. Shartle, eds. Occupational Counseling Techniques. N.Y.: American Book Co., 1940. p. 245-252, appendix V) which corrects for shrinkage in the multiple correlation is perhaps the only nonstandardized statistical parameter used in this evaluation. Future plans are to utilize magnetic tape for data storage of fixed format information and final analysis using a UNIVAC 418 computer.

The Atomic Bomb Casualty Commission Study
U.S. National Academy of Sciences
The Atomic Bomb Casualty Commission

The Atomic Bomb Casualty Commission (ABCC) is a joint activity of the U.S. National Academy of Sciences, under contract to the Atomic Energy Commission, and of the Japanese National Institute of Health. Laboratories are maintained in Hiroshima and Nagasaki.

Total staff consists of about 800 persons of which 770 are Japanese. About 48 of the 800 are professional level workers. The director of the project is Dr. George Darling.

In the more than 20 years of its existence, ABCC has performed a great number of studies relating to the effects of atomic radiation on humans. During FY 1966, some 72 different studies were in process. The following description relates only to studies which are of a longitudinal nature.

GOALS

The objective of the study is to learn all that is possible of the effects on man of exposure to ionizing radiation in a single dose ranging from a few to several hundred rad. Principal efforts include:

a) Effects on mortality and acceleration of aging.

b) Physiologic changes including those similar to the effects of aging.

c) Effects on chromosomal material as measured by the induction of chromosomal aberrations.

d) Effects on subsequent growth and development of those exposed in utero or in infancy or childhood.

e) Effects on incidence of diseases, including cancer.

SUBJECTS

The subjects include all residents obtainable who were exposed, plus a control group who were not. This population is broken down into:

1. Those within 2000 meters of the hypocenter of the atomic bomb explosion, divided into those who had acute radiation symptoms and those who did not.

2. Those 2000-2500 meters from the explosion.

3. Those 2500-10,000 meters from the explosion.

4. A control group who were not exposed.

These total about 100,000 subjects.

Most of the research has been done on the "clinical subsample" consisting of all of (1) above, plus equal members from groups (2), and (3) and (4), matched by sex, city and age.

VISIT INTERVALS

The clinical subsample is examined every other year. This was begun in 1958.

STUDIES PERFORMED

I. Master Sample

A. Information on exposure, shielding and estimated radiation dosage received.

B. Birth date, information on death, and findings of autopsy which is performed whenever possible.

II. Clinical Subsample

"A" and "B" above, plus

C. Biennial physical examination

1. Height and weight
2. Skinfold thickness
3. Hematology: hemoglobin, hematocrit, red-cell count, white-cell count, differential white count, sedimentation rate
4. Urinalysis: specific gravity, pH, glucose, protein, microscopic examination
5. Stool examination for blood, ova
6. Blood pressure
7. Chest x-ray
8. Questionnaire adapted from Cornell Medical Index (history and present symptoms)
9. Interview information: smoking, drinking, diet, occupational and residential facts

III. Portion of Clinical Subsample, Additionally

A. Chromosome studies (number and aberrations) in culture of lymphocytes

B. Cardiovascular disease studies on males, to match studies on Japanese ethnic groups in Hawaii and California

1. Grip strength and anthropometric measures
2. Vital capacity
3. 12-lead electrocardiogram
4. Serum cholesterol and uric acid
5. Serum triglycerides
6. Blood clotting and lysis
7. Ocular fundus photography

In addition, many small studies in this large system have employed a great variety of measures to test specific hypotheses.

DATA STORAGE

Information is placed on standard forms at the time of examination. It is then coded, punched on IBM cards, and entered on magnetic tape. Some data go from laboratory form directly to tape via an optical scanner.

The Master Sample tape record consists of 260 characters per subject.

The Clinical Sample tape consists presently of 1,400 characters per subject. It includes information on how to contact the subject and contact history.

Data from sub-studies on small sub-samples are handled in various ways. Some may be added to the Clinical Sample tape records for that examination cycle.

DATA ANALYSIS

Statistical approaches have been varied. Contingency-table analysis and analyses of variance and co-variance are used most frequently, with multiple regression, discriminate function analysis and factor analysis also used.

All biennial size measurements of children aged about 8 to 18 are fitted to a family of growth curves by an IBM 1440 computer. "Reasonably standard" computer routines are used in the various analyses of all data.

The Tecumseh Community Health Study
University of Michigan

The Tecumseh Community Health Study is conducted under a program project grant from the National Heart Institute and constitutes the key part of the Center for Research in Diseases of the Heart, Circulation and Related Disorders in the University of Michigan. The Study Staff includes a Director, Dr. Frederick H. Epstein, Associate Director, Mr. J. A. Napier, full-time physicians, biostatisticians and other professional staff, a field supervisor and team of interviewers, nurses and clinic technicians, as well as clerical, secretarial and laboratory personnel. There is an advisory Board of Scientific Directors composed of senior faculty members in the Schools of Public Health and Medicine, including the Deans of these two institutions; Dr. Thomas Francis, Jr., is Chairman.

Working relationships are maintained through formal and informal contact, meetings of the research staff as a whole and working groups among the staff for projects within the total project, as needed.

GOALS

The town of Tecumseh, Michigan, and its surrounding area was chosen to study a complete natural community including the population and its biological, physical, and social environment. It was intended to examine the entire population, recognizing that this would yield information on multiple disorders and their occurrence in the same population, identified as individuals, families and households. The long-range undertaking is based at the University of Michigan School of Public Health and Medical School. The broad view embraces not merely a maintenance of the Tecumseh facility and an examination program but also includes lines of biological and medical research directed toward the detection of early aberrations. Thus biochemical, physiological, immunological and genetic studies are included, along with a mapping of the environment. This network of integrated investigations in the field, laboratory, and clinic aims at studying the origins and causes of the major chronic disorders with particular emphasis on cardiovascular diseases, diabetes, chronic pulmonary disease, and arthritis.

The further purpose is to conduct investigations to determine the underlying defect, the precursor states, and to detect the early evidences of disorder with a view to seeking preventive measures. To gain proper information on all ages and sexes regarding origin and genesis of disorders requires a total community. Such a stable resource provides the potential means of carrying out

a large variety of epidemiological studies within the same setting over the years, to yield a comprehensive ecological picture of man. The data so available relate to multiple disorders rather than to a single category of disease. It is implicit in the concepts underlying the study that the Tecumseh community, viewed as an ecological unit of the population and its environment, will be under regular and continuing surveillance. These acitivites constitute the "Field Studies".

In conjunction with the field studies, "Supportive Research" of an exploratory nature encompasses specific, sharply focused investigations in the laboratory, clinic, and special subsegments of the Tecumseh population, aimed at discovering new investigative methods and basic mechanisms of etiology. The special studies are closely integrated with the field studies and are centered in the University clinics and laboratories as well as in the Tecumseh population, emphasizing studies of etiological factors in the genesis of the target disorders. They represent an extension of clinical and laboratory investigations on the epidemiological front and are not viewed as being separate from the field studies in Tecumseh but as an epidemiological operation in which field, laboratory, and clinical studies gain from the advantages of their reciprocal contributions.

A concentration of attention and exploratory research effort will relate to family groups comprising index cases, their close relatives and kindred controls in whom will be centered studies seeking information on the basic defects, their origin, and the causative factors responsible for them. The hypothesis is that the precursors of manifest disease and early signs of disease susceptibility are likely to be found among the close associates of the index case. The phase of community research provides the setting and basic information to identify and characterize index cases, controls, and their associates.

The results already obtained give assurance that such a study is feasible and can be maintained to yield a picture of a contemporary community in terms of biological -- and eventually -- social and physical interactions. The main hope, however, is that the intensive exploratory research integrated with these broad field activities will contribute to the recognition of etiological mechanisms with resultant applications in the prevention of chronic disease.

While not specifically designed as a study of aging, biological and social data on the same people of all ages observed at regular intervals within a defined, natural environment cannot help but provide information on changes over time in the absence and presence of disease. Indeed, it must be an objective of the study to differentiate, as far as this is possible, the features associated with aging per se from those which are influenced by

pathological lesions. One unique feature of the Tecumseh study is that the "healthy" cohort for the study of "normal" aging is not preselected but can be defined retrospectively in terms of subsequent disease events occurring in a representative base population.

SUBJECTS AND VISIT INTERVALS

The population of the town of Tecumseh and environs was first stratified into five regions of relative socio-economic homogeneity. The households in each of these five strata were divided into ten random samples. Thus, ten random samples of the entire population by dwelling units were formed. In this fashion the data from each of the ten random samples could be regarded as representative for the community at large.

During 1959-60 the entire population received medical examinations with a response rate of approximately 90%. The second cycle of examinations was conducted after an interval of an average of four years. A third cycle is in progress and will be completed in 1969. It is planned to re-examine the entire population, including newcomers, every two years in the future, according to an abbreviated examination schedule, relying mostly on a repetition of the tests which have been made over the past 10 years (see below).

Special examinations at selected intervals will be carried out in parallel among sub-samples of the population appropriate for detailed studies of coronary heart disease, diabetes and hyperglycemia, chronic respiratory disease and rheumatic diseases, using specialized tests in addition to those obtained for the population as a whole.

STUDIES PERFORMED

1. Medical history.
2. Physical examination; blood pressure by automatic recorder.
3. Electrocardiogram: Standard 12-lead orthogonal ("normalized" tracing according to McFee).
4. Chest x-ray.
5. Pulmonary function tests: Vital capacity, forced expiratory volume, volume and flow measurements, single breath nitrogen index of uneven ventilation.
6. Anthropometry: Height, weight, skinfolds, skeletal diameters.
7. Laboratory tests: Serum cholesterol, serum triglyceride, lipoprotein electrophoresis, blood sugar one hour after standard load (insulin levels in special groups), rheumatoid factor tests, serum uric acid, immunoglobulins, hematocrit, urinalysis.

8. Exercise physiology: Physical activity record by standardized questionnaire and treadmill test (measuring electrocardiogram, pulse rate, blood pressure, ventilation, oxygen-nitrogen-carbon dioxide exchange).
9. Genetic markers: 11 blood group and serum systems.
10. Viral and bacteriological studies of respiratory illnesses in random, rotating family samples.
11. Dietary questionnaires.
12. Standardized questionnaires to evaluate social and psychological characteristics and stresses.
13. Measurements of air pollution and water hardness.

DATA STORAGE

The data are coded, transferred to punch cards, and subsequently placed on tape using "master files" and "working files". Summary statistics in machine readable form are available, using data reduction methods as needed.

DATA ANALYSIS

The full scale analysis of the data consists of analyses both within and between rounds of examination. The within-round analyses include statistical description of distributions of attributes, study of interrelations among the quantitative variables, and study of relations between prevalence of disorders and potential risk factors. The between-round analyses include studies of stability of distributions, incidence data, and relations between incidence and the quantitative variables. Both univariate and multivariate approaches are in use.

The program of data analysis uses the unit record (punched card) equipment of the School of Public Health and the facilities of the University of Michigan Computer Center. The latter consist of an IBM 360 Model 67 computer, with the aid of a computer console in a time-sharing system (MTS, the University of Michigan Terminal System). Most computer programming is done in MAD but FORTRAN is also used.

Studies in Geriatric Mental Illness
Langley Porter Neuropsychiatric Institute

The "Studies in Geriatric Mental Illness" is an interdisciplinary project of psychiatrists, psychologists, social psychologists, sociologists and anthropologists conducted at the Langley Porter Neuropsychiatric Institute, University of California Medical Center, San Francisco. The study was started in 1958 and has been supported by Public Health Service Grant No. MH 09145 from the National Institute of Mental Health. Dr. Alexander Simon and Professor Marjorie Fiske Lowenthal (Director) are co-principal investigators.

GOALS

The overall objectives of the initial research in geriatric mental illness were to determine medical, psychological and sociological reasons why increasingly large proportions of older persons were finding their way into public mental hospitals; to contribute to further understanding of the spectrum of normal and abnormal aging processes; to trace the "natural history" of mental disorders in this older age group; and in light of the findings to make recommendations about care and treatment.

The unique features of the hospital sample allowed: a) a comparison of patients committed to mental hospitals with those discharged from psychiatric screening wards; b) an analysis of the course of illness from the time of hospitalization onward, as well as retrospectively; and c) detailed clinical, psychological, social and EEG data from the time of admission to the time of death, correlated with neuropathological findings.

The purpose of the community sample was to provide a group of community-resident aged representing a wide variety of socio-economic levels and living in census tracts having a complete range from those with highest to those with the lowest rates of admission to state hospitals (in this age group), thus furnishing a wide spectrum of aging patterns against which to view the hospital sample.

SUBJECTS

The sample bases for the study are: a) 534 persons aged sixty and over admitted to the psychiatric observation wards of San Francisco General Hospital in the calendar year 1959, constituting a near-universe of consecutive first admissions, excluding only persons with admissions prior to age sixty and persons

who did not meet the hospital's residence requirement of one year in San Francisco, and b) 600 persons sixty years and older living in the City of San Francisco stratified by age, sex and social living arrangements selected from the 18 census tracts having the highest proportion of elderly people.

CONTACT INTERVAL

Both the hospital and community samples were interviewed at three points in time at approximately annual intervals.

	Hospital Sample	Community Sample
	N	N
Baseline	534	600
First year follow-up	287	440
Second year follow-up	247	288

Three years following admission a subsample of both the hospital (N=40) samples were administered intensive life history interviews and given psychological tests. This was followed by a medical/psychiatric examination (including laboratory tests) in year four.

A mailed questionnaire to hospital psychiatrists was completed in year five for those hospital sample subjects still in state hospitals.

STUDIES PERFORMED

Studies performed fall into the following categories: socio-economic, demographic, roles and activities, physical and social self-maintenance, psychological, physical health condition, interview characteristics, collateral information and responses to open-ended narrative questions (such as self-image, stressful events, pleasant periods, desired life changes in retrospect, daily activities, best age to be, plans and expectations).

Roles and activities included inquiries on kin, friends, household composition and confidant and social participation. Psychological items included self-reported symptoms, tested intellectual functions (digit span, Kent EGY, memory test), interviewer reported symptoms and attitudes and perceptions.

Physical health condition covered self-reported illnesses and health problems obtained from a health questionnaire given by the social interviewer. A medical examination schedule was

administered by a physician for the hospital sample and for a subsample of the community sample; laboratory tests, EEG's, post mortem studies were also obtained.

Indices have been developed for rating physical and social self-maintenance, degree of psychiatric and physical disability, socioeconomic status and morale.

DATA STORAGE

A comprehensive body of sociological, psychological and clinical data, both structured and open-ended, were gathered from the subjects (both hospital and community) and from their collaterals as well. Additional data were obtained from the San Francisco General Hospital charts, State hospital charts, death certificates, post mortem reports, laboratory tests, and psychological tests.

For each subject there are folders of original and abstracted data, which vary by subject but may include any of the above-mentioned data. Master control listings are available for schedules, tests and the various miscellaneous data available for each subject, for the various points of contact. Statistical tabulations, cross-runs, listings and tables are available. Unstructured open-ended material for the intensive life history material has been topically coded; history of illness schedules reflecting chronological development of events leading to hospitalization for the hospital sample subjects have been prepared.

All coded data were originally key-punched. This has recently been transferred to magnetic 8980 computer tape for storage.

DATA ANALYSIS

Data have been subjected to both qualitative and quantitative analysis including descriptive statistics, standard, summary and cluster scores, factor analysis, content analysis of open-ended material using topical codes, protocol ratings, and analysis of change through time.

PUBLICATIONS

Three books and 47 articles have been published; list available on request. A monograph, Crisis and Intervention, accepted for publication, is now being completed.

The following schedules were completed by psychiatrists, psychologists, and/or social interviewers; however, some were given to the hospital sample and not the community sample, and were varied, modified, or deleted at different rounds of interview:

Activity Scale
Case Summary Sheet
Chart Review (San Francisco General Hospital)
Deceased Patient Medical Schedule
General Schedule - Subject
General Schedule - Collateral
Health Schedule
History of Illness
Intensive Life History Interview - Social
Intensive Life History Interview - Medical
Kent E-G-Y
Medical Data Summary Sheet and Supplement
Medical Schedule
Narrative Report of Social Interview
Practical Functioning Scale
Profile Summary
Psychiatrist's Worksheets
Psychological Rating Data Sheet
Psychological Summary Data Sheet
Ratings of Physical and Psychological Disability
WAIS

The USAF Aerospace Medical Fitness Program
United States Air Force

The Aerospace Medical Fitness Program (AMF) has been in existence at the USAF School of Aerospace Medicine since July 1965. This institution is located at Brooks Air Force Base in Texas. The project scientist is Timothy N. Caris, Colonel, USAF (MC) and the task scientist is Lawrence J. Enders, Major, USAF (MC). Data processing and analysis are performed by the Biometrics Division of the USAF School of Aerospace Medicine headed by M. Bryan Danford, Ph. D.

GOALS

Utilizing periodic medical evaluations of rated personnel and taking advantage of modern data storing, retrieval and analysis techniques, our objectives are:

a. To delineate the effects of biologic aging.

   (1) Provide longitudinal and cross-sectional data as a foundation for developing new and more encompassing standards for selection and maintenance of the Air Force flying population on valid statistics.

b. Define more clearly the natural history of the development of disease states and disorders in an initially healthy population.

   (1) Provide additional knowledge and stimulate development of techniques and methods for earlier and more accurate diagnosis.

   (2) Improve predictive capabilities for identification of individuals with potential problems.

   (3) Define the influence of various developing disorders on aircrew effectiveness, flight safety, and health maintenance and disability of Air Force rated personnel.

c. To identify significant problem areas in health originating in the field which have particular importance to the aerospace mission.

   (1) Provide stimulus for research scientists to direct their efforts in these mission-oriented problems.

   (2) Provide direction to the teaching and training of personnel who will be handling aerospace medical problems at base level.

SUBJECTS

The program is based on both cross-sectional as well as longitudinal studies on both completely healthy populations and smaller groups of individuals with suggestions of or distinctly early signs of disease (with matched controls). There are three distinct categories.

a. All personnel in the USAF rated as flyers are entered into the program at such time as they reach their 30th, 35th, 40th, or 45th birthday. Within five years all individuals will be subjects, and from that point on all additional flyers (except those in Categories 2 and 3 below) will enter the program upon reaching 30 years of age. The historical events, physical findings and laboratory data included in the present annual physical examination requirements (Forms 88 and 89 included as Attachments 1 and 2) will be utilized. In addition, annual serum determinations of cholesterol, triglycerides, phospholipids, total protein, albumin, urea nitrogen, uric acid, creatinine, calcium, and inorganic phosphorus will be performed on all subjects at the clinical laboratories at USAF SAM.

b. Similarly all graduates of the USAF Military Academy, providing men of an earlier age (20 years) than the above at onset will be entered into the program. The baseline studies in this group will include all factors listed in Category 1, but in addition, there will be a much more detailed history, Form 81 (Attachment 3), tonography, tonometry, colored photographs of optic fundi, electroencephalogram, pulmonary functions (maximum breathing capacity and vital capacity), plasma recalcification time and plasma glucose level two hours after drinking 100 grams of glucose in water.

   Those academy graduates who enter flying careers will be followed longitudinally. They as well as those in Category 1 will be required to undergo annual evaluations by their flight surgeons, and a copy of the Standard Forms 88 and 89 will be furnished to the AMF program.

c. This category includes specialized projects initiated at USAF SAM and requiring specialized skills, diagnostic tools, and techniques not readily available at all USAF medical facilities (e.g., cardiovascular responses to treadmill exercise, accelerative forces, and orthostasis, phonocardiography, apexcardiography, vector cardiography, myocardial perfusion as determined by rubidium - 84 uptake,

electroencephalography under stress, psychometric testing, and other pertinent methods as they are identified.

These longitudinal studies are being performed on healthy subjects as well as those with early disease or suggestion of disorder. These groups do not deal in the great number of participants characteristic of the first two categories, but are designed to yield statistically valid results.

PRESENT STATUS

Obviously an undertaking as complex as the AMF program requires frequent reappraisals, particularly at the onset. After two and one half years of experience we have done just that. Some initial benefits include the cross-sectional development of norms at various age groups for serum chemistry levels and detailed compilation of past history, social history and family history of over 12,000 subjects. The electroencephalographic data already have permitted us to identify normal variants not previously recognized as such. We have completed coding approximately 700,000 electrocardiograms (10 year serial tracings being available at this time in over 12,000 males) so that the earlier established ECG Repository Project (initiated in 1957) is being assimilated into the AMF program. The value of this ECG undertaking has provided valuable knowledge already and is well-documented in the general medical literature. Its value should continue to grow progressively.

In our appraisal, we have identified specific problem areas -- logistic, personnel, financial and technical. Attempts at appropriate solutions are underway. We consider our present status to be similar to that of a prototype design. Although we have projects of scientific value under way, we are still in a stage of performing quality control and in a period when we are learning to live with the system.

Federal Aviation Administration
Air Traffic Controller Health Program
Federal Aviation Administration

This program began in 1965 and is conducted by the Federal Aviation Administration under the direction of Peter V. Siegel, M.D., Federal Air Surgeon. Responsibility for policy development has been delegated to Hayden W. Withers, M.D., Chief, Aeromedical Services Division. The Regional Flight Surgeons are responsible for conducting the program in their respective regions.

GOALS

The primary goal is the enhancement of air safety through the detection and correction of physical deficiencies among the air traffic control specialists in the United States. Where correction is not possible, and the condition may be expected to incapacitate the employee thereby jeopardizing aviation safety, reassignment or medical retirement is recommended.

A secondary goal is the maintenance of health and productivity among the air traffic control employees, a group under extreme stress and in short supply.

SUBJECTS

The subjects participating in the program are highly motivated federal government employees, primarily male, most with high school educations and experience in the aviation field. Approximately 12,500 such employees ranging in age from twenty to sixty participate in the program annually. They are employed in the air traffic control towers that direct the takeoffs and landings of aircraft at airports, and at the air traffic control centers that direct the path of the aircraft from airport to airport.

EXAMINATION INTERVALS

All employees actively controlling air traffic are required to undergo the examination prior to entrance on duty and annually thereafter.

STUDIES PERFORMED

1. Sixteen Personality Factors Psychological Test. This is a psychological screening test. Employees or candidates with high anxiety indices are referred for additional psychiatric and psychological evaluations. Annual performance of this test is planned, but administrative difficulties have prevented repetition. Initial tests have been obtained on all active controllers though.

2. Chest X-ray annually.

3. Pure tone audiogram annually.

4. EKG annually.

5. Complete history-physical examination annually.

6. Specialty evaluations as indicated for conditions detected by above examinations.

DATA STORAGE

Information obtained through the 16 Personality Factors tests is recorded on IBM punch cards. Information obtained through the remainder of the examinations is recorded on magnetic tapes. The magnetic tapes contain similar information on the entire active airman population in the United States.

DATA ANALYSIS

An annual printout is produced indicating pathology detected by age and status. Detailed information relative to specific pathology, specific age groups, and specific location of employment can be extracted from the computer tapes as required.

APPENDIX D: FISCAL ANALYSIS OF RESEARCH ON AGING

The sum expended on research programs on aging in fiscal year 1967 was $14,130,658. The sum expended on longitudinal studies that were directly or tangentially concerned with aging processes was $3,041,610. However, only $1,262,116 of this later sum was not included in the figure for research program expenditures given above.

The components* of the research program expenditures by the individual agencies were:

National Institute of Child Health and Human Development	$4,979,942
National Institute of Mental Health	2,040,820
Bureau of Health Services	2,890,466
Atomic Energy Commission	2,991,724
Veterans Administration	1,227,706
	$14,130,658

An analysis of each research program by individual grant is given next.

*These figures differ from figures that have previously been quoted by the involved Government agencies because the criteria used in their selection were different. An attempt was made in this review to include only those projects that bore directly on aging processes or on problems that were unique to the aged. Research that dealt with disease processes that were important to all adults but not unique to the elderly was not included.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

EXTRAMURAL

Grant Number	Principal Investigator	Expenditure
HD 00041	Getty	$30,480
HD 00042	Brandes	33,035
HD 00086	Ross	94,920
HD 00146	Brand	25,641
HD 00261	Rockstein	23,373
HD 00340	Talland	14,553
HD 00364	Lieberman	42,185
HD 00407	Jones	13,101
HD 00490	Ross	33,321
HD 00494	Zorzoli	16,435
HD 00510	Wickstrom	11,337
HD 00517	Jones	25,566
HD 00518	Proper	158,370
HD 00518-S1	Proper	36,104
HD 00534	Walford	58,686
HD 00571	Rockstein	30,465
HD 00599	Tobis	55,183
HD 00636	Ewing	26,305
HD 00642	Weil	35,616
HD 00643	Randall	30,672
HD 00648	Weiss	22,415
HD 00668	Busse	365,247
HD 00669	Kohn	225,501
HD 00670	Ring	72,518
HD 00671	Martel	128,142
HD 00672	Steele	90,632
HD 00674	Deming	342,963
HD 00703	Chang	27,712
HD 00769	Homburger	18,276
HD 00853	Ehrenkranz	0
HD 00977	Harman	5,760
HD 00988	Gottlieb	17,640
HD 01066	Snyder	13,523
HD 01179	Andrew	25,326
HD 01186-S1	Scott	1,412
HD 01186	Scott	12,412
HD 01274	Donahue	118,569
HD 01325	Botwinick	19,616
HD 01491	Miras	6,800
HD 01502	Tsaltas	27,006
HD 01550	Goldstein	16,433
HD 01615	Jarvik	61,961
HD 01691	Griew	4,424

Grant Number	Principal Investigator	Expenditure
HD 01735	Rhudick	63,756
HD 01757	Britton	16,773
HD 01833	Glass	13,276
HD 01971	Sallman	28,473
HD 01989	Brinley	4,307
HD 02033	Tappen	37,834
HD 02102	Schaie	2,952
HD 02119	Felts	26,912
HD 02191	Kabara	26,197
HD 02194	Anderson	231
HD 02207	Snook	13,070
HD 02217	Jenkins	16,999
HD 02250	Inglis	36,688
HD 02261	Strebel	62,255
HD 02377	Sinex	20,668
HD 02416	Adams	45,076
HD 02513	Hausknecht	20,904
HD 02558-A1S1	Bergman	7,017
HD 02558	Bergman	32,644
HD 02566	Wachsman	28,220
HD 02582	Peak	8,196
HD 02586	Simonson	15,960
HD 02612	Selye	47,650
HD 02646	Meyer	77,661
HD 02718	Forbes	19,429
HD 02721	Cristofalo	28,458
HD 02741	Lansing	44,880
HD 02741-S1	Lansing	12,124
HD 02888	Swendseid	29,033
HD 02919	Lindsay	26,520
	TOTAL	$3,233,799
NICHD - Intramural*		$1,746,143
NICHD - Total		$4,979,942

*The accounting procedures of this program do not break down expenditures by research project.

NATIONAL INSTITUTE OF MENTAL HEALTH

EXTRAMURAL

Grant Number	Principal Investigator	Expenditure
MH 01981	Kluver	$52,633
MH 04591	Robins	71,940
MH 06022	Shmavonian	26,441
MH 08060	Lehman	24,250
MH 08061	Leibowitz	24,099
MH 08534	Spitzer	94,283
MH 08556	Buschke	19,477
MH 09145	Simon	181,736
MH 10359	Samuels	51,908
MH 10895	McHugh	19,512
MH 10927	Feinberg	76,590
MH 11668	Engel	151,140
MH 12132	Gordon	61,387
MH 12400	Antonovksy	23,530
MH 12492	Anderson	17,465
MH 13434	Eriksen	4,200
MH 13460	Wang	4,200
MH 13682	Herrmann	4,110
MH 13821	Kleban	4,200
MH 14423	Gaitz	88,280
MH 14832	Stotsky	23,898
MH 14881	Wilner	75,313
MH 14888	Wylie	4,693
MH 14889	Kastenbaum	41,551
MH 14893	Hall	61,140
MH 14894	Donahue	116,485
MH 14902	McKain	9,125
MH 14915	Thune	25,647
MH 14917	Carey	107,838
MH 14923	Powell	94,485
MH 14924	Blackburn	98,080
MH 14926	Nathanson	64,240
MH 15020	Hamovitch	119,454
MH 15047	Brody	75,403
MH 15075	Granick	58,466
MH 08315	Clausen (Institute of Human Development Studies)	36,110
MH 05300	Clausen	27,511
		$2,040,820

BUREAU OF HEALTH SERVICES

EXTRAMURAL

Grant Number	Principal Investigator	Expenditure
CH 00249	Colombotos	$46,423
CH 00329	Babchuk	31,009
CH 00362	Fowler	72,284
CH 00363	Parker	0
CH 00384	Pihlblad	36,528
CH 00385	Blenkner	145,697
CH 00386	Richardson	200,374
CH 00392	Friedman	170,145
CH 99006	Trager	184,316
CH 89488	Pirri	48,000
CH 34997	Woodside	69,923
CH 59458	Lane	128,321
CH 23-26	May	79,148
CH 27-23	Slattery	150,580
CH 34-48	Torrons	89,161
CH 29436	Manheimer	52,331
CH 29434	Johnson	65,252
CH 37-19	Little	74,870
PH 108-66-189	Irish	40,717
PH 108-66-233	Barbaccia	204,389
PH 108-66-281	Krumbiegel	211,033
PH 110-67-21	Ward	27,300
PH 108-67-39	Crooks	2,375
PH 108-67-41	Gitman	134,142
PH 110-67-65	Gravel	207,272
PH 108-67-66	Glasser	55,936
PH 110-67-83	White	52,780
PH 108-67-94	Crooks	3,700
PH 108-67-96	Robben	18,460
PH 110-67-100	Howell	17,000
PH 110-67-148	Lewis	38,430
PH 110-67-185	Roney	79,240
PH 110-67-216	Letcher	60,660
PH 110-67-217	DeFries	24,900
PH 110-67-231	Wright	26,400
PH 110-67-238	Mosher	17,800
PH 110-67-239	Di Jioia	23,570
		$2,890,466

ATOMIC ENERGY COMMISSION

Grant Number	Principal Investigator	Expenditure
AT(04-1)-GEN-12	Bennett	$47,000
AT(04-1)-GEN-12	Mead	90,000
AT(11-1)-34	Wood	48,000
AT(11-1)-1474	Brizzee	50,000
AT(30-1)-1243	Dobyns	10,847
AT(30-1)-2071	Brent	31,000
AT(30-1)-3314	Yuhas	78,083
AT(30-1)-3394	Mancuso	130,000
AT(30-1)-3518	Wulff	30,000
AT(30-2)-GEN-16	Curtis	138,000
AT(45-1)-581	Koler	93,000
AT(49-1)-GEN-72	Darling	463,000
AT(49-1)-GEN-72	Darling	287,500
W-31-109-ENG-38	Sacher	197,000
W-31-109-ENG-38	Sacher	239,000
W-7401-ENG-49	Baxter	66,729
W-7401-ENG-49	Casarett	137,565
W-7401-ENG-49	Casarett	34,000
W-7405-ENG-26	Makinodan	120,000
W-7405-ENG-26	Upton	614,000
W-7405-ENG-48	Durbin	87,000
		$2,991,724

VETERANS ADMINISTRATION

Principal Investigator	Expenditure
Abt	$11,234
Anday	NA*
Apfeldorf	20,303
Apfeldorf	3,807
Barboriak	16,864
Bell	20,000
Bell	5,500
Bell	11,375
Bell	19,000
Bell	40,000
Bell	30,000
Bortner	NA
Bortner	NA
Brochu	2,595
Buchanan	20,000
Canestrari	NA
Canestrari	NA
Capers	11,826
Cherkin	82,920
Cleveland	2,085
Coleman	29,060
Conner	NA
Coppinger	NA
Davis	37,577
Dolson	16,818
Edwards	8,350
Fisher	12,000
Frenkel	10,085
Haining	62,365
Hoch	36,017
Hogan	NA
Huemer	47,900
Jakubzak	37,797
Koenig	4,000
Lindsay	10,257
Lindeman	1,611
Linn	18,852
McGavack	10,000
McGavack	5,000
McGavack	12,207
McGavack	12,207
Magid	1,295
Murray	13,401
Naumann	5,084
Needleman	4,250
Phillips	13,052

VETERANS ADMINISTRATION (Continued)

Principal Investigator	Expenditure
Piko	$80,053
Pishkin	400
Rich	3,000
Schlenker	9,720
Schwartz	51,570
Sekhon	24,838
Sinex	28,889
Simon	NA
Sklar	6,000
Smith	500
Sobel	76,214
Soldo	28,423
Stidworthy	37,804
Thornton	39,891
Tice	6,763
Walter	38,677
White	15,048
Wang	35,837
Yu	37,385
Albacete	
Pipberger	NA
Freis	
	$1,227,706

* Not Available

The funds expended on longitudinal studies in fiscal year 1967 were:

Study	Agency	Expenditure
Longitudinal Program of the Gerontology Research Center Baltimore, Maryland	NICHD	$250,000
Study of Physiologic and Psychologic Aging in Pilots Lovelace Foundation Albuquerque, New Mexico	NICHD	158,370
Normative Aging Study Veterans Administration Boston, Massachusetts	VA	125,875
Longitudinal Study of Aging Duke University Durham, North Carolina	NICHD	45,876
Human Aging Project Philadelphia Geriatric Center Philadelphia, Pennsylvania	NIMH	58,466
Intellectual Functioning in Later Life Age Center of New England Boston, Massachusetts	NICHD	63,756
Institute of Human Development Studies University of California Berkeley, California	NIMH	63,621
Brown University Longitudinal Study of Aging Brown University Providence, Rhode Island	NICHD	128,142
Consistency of Personality and Adjustment in Old Age Pennsylvania State University University Park, Pennsylvania	NICHD	16,773
Pensacola Study of Naval Aviators Naval Aerospace Medical Institute Pensacola, Florida	United States Navy	1,000

Studies in Geriatric Mental Illness Langley Porter Neuro-psychiatric Institute San Francisco, California	NIMH	$181,736
Atomic Bomb Casualty Commission Study Hiroshima, Japan	AEC	750,500*
Tecumseh Community Health Study University of Michigan Ann Arbor, Michigan	NHI	589,295
USAF Aerospace Medical Fitness Program USAF School of Aerospace Medicine Brooks Air Force Base, Texas	USAF	20,000**
FAA Air Traffic Controller Health Federal Aviation Administration Washington, District of Columbia	FAA	588,200

The expenditures for the longitudinal studies include some funds already included under the research programs. The funds not recorded under research programs are those for the Institute of Human Development Studies, the Tecumseh Study, the Pensacola Study, the Aerospace Medical Fitness Program, and the FAA Air Traffic Controller Health Program. The funds for those total $1,262,116. A major component of this money is the funds ($588,200) for the FAA study. That money was spent to provide a necessary service to the nation.

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* Aging research component only (Total study - $3,500,000).
** Aging research component only.